MAJOR ARTICLE

Comparison of Risk Factors for Human Metapneumovirus and Respiratory Syncytial Virus Disease Severity in Young Children

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Background. Human metapneumovirus (hMPV) and respiratory syncytial virus (RSV) are leading pediatric pathogens. However, risk factors for severe hMPV disease remain unknown. We comparatively assessed environmental, host, and viral determinants for severe hMPV and RSV infections.

Methods. We studied a prospective cohort of >1000 children aged <3 years hospitalized in or presenting to a pediatric clinic for acute respiratory infection. We collected clinical data at enrollment and 1-month follow-up and tested nasopharyngeal secretions for respiratory viruses. Disease severity was defined as hospitalization and was also assessed with a severity score (1 point/variable) calculated on the basis of fraction of inhaled $O_2 \geq 30\%$, hospitalization >5 days, and pediatric intensive care unit admission.

Results. hMPV was identified in 58 of 305 outpatient children (19.0%) and 69 of 734 hospitalized children (9.4%), second only to RSV (48.2% and 63.6%, respectively). In multivariate regression analysis of hMPV cases, age <6 months and household crowding were associated with hospitalization. Among hospitalized patients, risk factors for severe hMPV disease were female sex, prematurity, and genotype B infection. Age <6 months, comorbidities, and household crowding were risk factors for RSV hospitalization; breast-feeding and viral coinfection were protective. Age <6 months and prematurity were associated with severe RSV cases among hospitalized children.

Conclusions. hMPV and RSV severity risk factors may differ slightly. These findings will inform hMPV prevention strategies.

Acute respiratory tract infection (RTI) is the second leading cause of death in children aged <5 years worldwide [1]. Among respiratory pathogens, the recently discovered human metapneumovirus (hMPV) figures prominently, being responsible for 10%–15% of pediatric hospitalizations for bronchiolitis and pneumonia [2]. hMPV is very closely related to respiratory syncytial virus (RSV) [3], the most important cause of RTI in young children [4]. Hospitalization due to hMPV and RSV is highest in infants, with annual hospitalization rates among those aged 0–5 months recently estimated to be 4.9 cases/1000 children and 17 cases/1000 children, respectively [5, 6]. In the United States alone, 51 000–82 000 infants are hospitalized annually with RSV bronchiolitis, generating an economic burden between $365 million and $585 million [7, 8].

Children with a history of prematurity and other chronic comorbidities are at increased risk for severe RSV disease [6, 9, 10]. Defining such high-risk groups permitted the design of immunoprophylaxis programs effective at reducing RSV hospitalizations through the targeted use of palivizumab, a monoclonal antibody. More recently, environmental factors such as exposure to smoking have also been incorporated into risk-assessment tools for RSV prophylaxis [11, 12].

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Furthermore, it has been suggested that viral factors such as genotype may influence RSV disease severity, although this remains controversial [10, 13].

Recent advances in the areas of hMPV vaccines [14], monoclonal antibodies [15], and antivirals [16] warrant the characterization of hMPV disease severity determinants for the rational development of preventive and therapeutic strategies among high-risk children. We hypothesize that, in a manner similar to RSV, there are specific host, environmental, and viral risk factors for severe hMPV RTI. However, few data exist regarding such factors, as earlier studies have focused on hMPV epidemiology and clinical manifestations [5, 17, 18]. Thus, we performed a study that aimed to prospectively evaluate hMPV disease severity determinants among hospitalized and community cases aged <3 years and to compare them to those for RSV.

METHODS

Study Setting

Quebec City, Canada, has a population of 512 000 inhabitants, including 93 100 children aged <18 years [19]. The Centre mère-enfant du Centre hospitalier universitaire de Québec (CHUQ) is the pediatric reference center for the Quebec City area, and the Sainte-Foy clinic is the largest pediatric primary care clinic for this city.

Study Design

We performed a prospective cohort study among children aged 0–35 months in Quebec City during 4 consecutive winter seasons, from 2006–2007 through 2009–2010. Patients were recruited from November to April inclusively, with the exception of 2009–2010, when recruitment was delayed until December because of resource reallocation associated with pandemic 2009 A/H1N1 influenza. The study was approved by the CHUQ research ethics committee.

Eligible participants were children that either (1) presented as outpatients to the Sainte-Foy pediatric clinic or (2) were hospitalized at the CHUQ for symptomatic acute RTI. Outpatients were required to manifest signs/symptoms of lower RTI, defined as the presence of cough and either fever (≥38°C) or suggestive findings on auscultation (rales/wheezing). Potential clinic subjects were identified by treating physicians trained regarding selection criteria and had a nasopharyngeal aspirate (NPA) collected.

Hospitalization was defined as admission for >24 hours to a short-stay unit, pediatric ward, or pediatric intensive care unit (PICU). Hospitalized subjects were identified by daily review of a registry of all NPAs, which are collected routinely in children hospitalized with RTI at this hospital.

Children were excluded if their RTI symptoms were of >7 days duration at recruitment, if they had been hospitalized in the preceding 14 days, or if they did not have a NPA collected within 24 hours of presentation. Study nurses enrolled patients from Monday to Friday. Eligible patients who presented twice for distinct episodes of RTI were counted as 2 cases.

In both settings, after written informed consent was obtained, standardized questionnaires were administered to the patient's parents/guardians at enrollment and at a 1-month follow-up telephone interview. In addition, medical records of hospitalized subjects were reviewed after discharge, and data were extracted using the same questionnaire. Specifically, we recorded demographic data, clinical signs and symptoms, preexisting medical conditions, vaccination history, environmental exposures, laboratory and imaging results, medical management (including treatments, requirement for supplemental oxygen, and PICU admission), and 30-day outcomes.

Virological Testing

NPA samples were promptly delivered to the CHUQ regional reference virology laboratory. Aliquots used for this study were stored at −80°C until further testing. Nucleic acids were extracted from 200 μL of thawed specimen using the QIAamp Viral RNA Mini Kit (QIAGEN, Mississauga, Canada). Reverse transcription was performed on the extracted material, using random primers (Amersham, Piscataway, NJ) and the Superscript II RT Kit (Invitrogen, Carlsbad, CA). A multiplex polymerase chain reaction (PCR)/DNA microarray hybridization assay was used to detect hMPV genotype A (hMPV-A), hMPV genotype B (hMPV-B), RSV genotype A (RSV-A), RSV genotype B (RSV-B) and 20 other respiratory viruses (Infiniti RVP assay, Autogenomics, Carlsbad, CA) [20], including adenoviruses, coronaviruses, enterovirus/rhinoviruses, influenza virus A/B, and parainfluenza viruses. A modified version of this method, capable of also indentifying pandemic 2009 A/H1N1 influenza virus, was used in 2009–2010. The research assistant performing study assays was blinded to clinical diagnostic test results.

Outcomes

Our primary outcome was disease severity, which was defined in 2 ways. First, we considered hospitalized children to have severe illness, compared with pediatric clinic patients. Second, among hospitalized subjects, we used a severity index established for RSV a priori, assigning 1 point to each of the following items: use of supplemental oxygen (fraction of inhaled $O_2 \geq 0.3$), PICU admission, and hospital stay >5 days [13]. Because very few (ie, 3) hMPV patients had a severity score of ≥2, we dichotomized our severity index as 0 and ≥1 for analysis of this subgroup. In contrast, 83 RSV patients had a score of ≥2, thereby allowing us to dichotomize the index to <2 and ≥2 for RSV in order to better characterize greater disease severity.

Data Analysis

Proportions and distributions were compared using the χ^2 test or the Fisher exact test; continuous values were analyzed using

the Student t test or the Wilcoxon rank-sum test. Statistical significance was assessed using 2-tailed tests, with an α of 0.05. No correction for multiple testing was considered. For comparative analyses of hMPV and RSV characteristics, children coinfected with both viruses (7 hospitalized patients and 6 outpatients) were excluded.

Univariate and multivariate logistic or log-binomial regression analyses, as appropriate, were performed to examine the association between risk factors and the primary study outcome, disease severity; relative risks (RRs), adjusted odds ratios (ORs), and 95% confidence intervals (CIs) were calculated. Variables with a univariate P value of $\leq$.2 and potential confounding factors were considered for inclusion in multivariable logistic regression models. Analyses were performed using Statistical Analysis Systems software, version 9.2 (SAS, Cary, NC).

RESULTS

From 2006 through 2010, 319 eligible clinic patients were approached: 5 refused participation, 9 were unreachable for the 1-month follow-up, and 305 completed the study. Figure 1 details the recruitment of hospitalized children, of whom 734 were studied. Therefore, 1039 episodes of RTI were analyzed (305 in the clinic and 734 in the hospital).

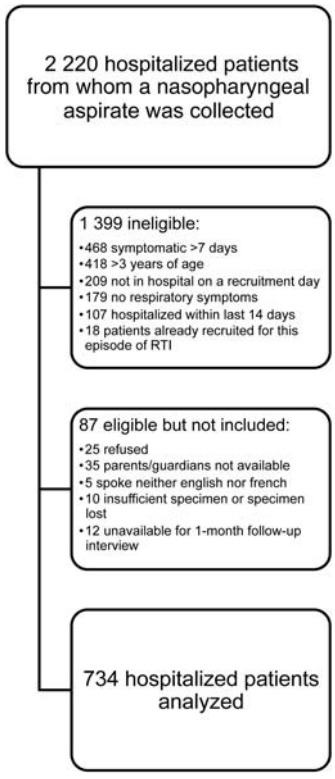

Figure 1. Flow diagram of study recruitment for hospitalized patients. Abbreviation: RTI, respiratory tract infection.

PCR/DNA Hybridization Microarray Testing

RSV was the most frequently identified virus in both hospitalized and clinic patients, with detection in 467 of 734 respiratory specimens (63.6%) and 147 of 305 respiratory specimens

Table 1. Results of Multiplex Polymerase Chain Reaction and DNA Hybridization Microarray Testing of Nasopharyngeal Aspirate Specimens From Patients in the Hospital or Clinic

Viruses Identified	Total, No. (%) (n = 1039)	Hospital, No. (%) (n = 734)	Clinic, No. (%) (n = 305)	P[a]
RSV[b]	614 (59.1)	467 (63.6)	147 (48.2)	<.001
RSV-A	344 (33.1)	259 (35.3)	85 (27.8)	.020
RSV-B	278 (26.7)	214 (29.2)	64 (21.0)	.007
hMPV	127 (12.2)	69 (9.4)	58 (19.0)	<.001
hMPV-A	62 (5.9)	35 (4.7)	27 (8.8)	.014
hMPV-B	65 (6.2)	34 (3.6)	31 (10.1)	.002
Influenza virus	34 (3.3)	21 (2.6)	13 (4.2)	.25
Influenza virus A	28 (2.7)	17 (2.3)	11 (3.6)	.29
Influenza virus B	6 (0.5)	4 (0.5)	2 (0.6)	1.00
PIV	43 (4.1)	22 (3.0)	21 (6.9)	.006
PIV-1	7 (0.7)	4 (0.5)	3 (0.9)	.43
PIV-2	3 (0.3)	2 (0.2)	1 (0.3)	1.00
PIV-3	33 (3.2)	16 (2.2)	17 (5.5)	.006
PIV-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Adenovirus	84 (8.1)	35 (4.8)	49 (16.1)	<.001
Adenovirus B	4 (0.4)	2 (0.3)	2 (0.6)	.59
Adenovirus C	52 (5.0)	21 (2.8)	31 (10.1)	<.001
Nontypeable	28 (2.7)	12 (1.6)	16 (5.2)	.002
Enterovirus/ rhinovirus	82 (7.9)	55 (7.5)	27 (8.8)	.45
Enterovirus A	2 (0.2)	0 (0.0)	2 (0.6)	.09
Enterovirus B	2 (0.2)	1 (0.1)	1 (0.3)	.50
Enterovirus C	0 (0.0)	0 (0.0)	0 (0.0)	NA
Enterovirus D	1 (0.1)	1 (0.1)	0 (0.0)	1.00
Rhinovirus A	51 (4.9)	33 (4.5)	18 (5.9)	.35
Rhinovirus B	1 (0.1)	1 (0.1)	0 (0.0)	1.00
Nontypeable	25 (2.4)	19 (2.6)	6 (1.9)	.66
Coronavirus	83 (8.0)	44 (6.0)	39 (12.8)	<.001
OC43	51 (4.9)	21 (2.8)	30 (9.8)	<.001
229E	3 (0.3)	0 (0.0)	3 (0.9)	.025
NL63	16 (1.5)	10 (1.3)	6 (1.9)	.58
HKU1	15 (1.4)	13 (1.7)	2 (0.6)	.25
Any virus identified	908 (87.4)	632 (86.1)	276 (90.1)	.06
0 virus	131 (12.6)	102 (13.9)	29 (9.5)	<.001[c]
1 virus	752 (72.4)	546 (74.4)	206 (67.5)	<.001[c]
>1 virus	156 (15.0)	86 (11.7)	70 (22.9)	<.001[c]

Abbreviations: hMPV, human metapneumovirus; NA, not applicable; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

[a] Comparing proportion of hospitalized vs clinic patients infected with that virus.

[b] Eight patients were coinfected with RSV-A and RSV-B.

[c] Global P value of χ^2 test comparing multiple proportions.

Table 2. Baseline Characteristics of Patients in the Hospital or the Clinic, Overall and by Infecting Pathogen

Characteristic	Total, Hospital (n = 734)	Total, Clinic (n = 305)	P[a]	hMPV,[b] Hospital (n = 62)	RSV,[b] Hospital (n = 460)	P[c]	hMPV,[b] Clinic (n = 52)	RSV,[b] Clinic (n = 141)	P[d]
Age (mo)									
<6	378 (51.5)	62 (20.3)	<.001[g]	18 (29.5)	270 (58.6)	<.001[g]	7 (13.6)	30 (21.3)	<0.16[g]
6–11	150 (20.4)	98 (32.1)	<.001[g]	23 (37.7)	77 (16.7)	<.001[g]	17 (32.7)	45 (31.9)	<0.16[g]
12–17	94 (13.0)	68 (22.3)	<.001[g]	11 (18.0)	48 (10.4)	<.001[g]	13 (25.0)	31 (22.0)	<0.16[g]
18–23	57 (8.0)	50 (16.4)	<.001[g]	5 (8.2)	32 (6.9)	<.001[g]	8 (13.4)	23 (16.3)	<0.16[g]
24–29	32 (4.3)	18 (6.0)	<.001[g]	2 (3.2)	21 (4.6)	<.001[g]	3 (5.8)	11 (7.8)	<0.16[g]
30–35	23 (3.1)	9 (3.0)	<.001[g]	2 (3.3)	13 (2.8)	<.001[g]	4 (7.7)	1 (0.7)	<0.16[g]
Mean ± SD	8.7 ± 8.5	12.8 ± 7.4	<.001	10.5 ± 7.7	8.0 ± 8.4	<.001	14.1 ± 8.0	12.5 ± 7.2	.22
Median (IQR)	5.7 (1.8–13.3)	11.7 (6.9–18.0)	NA	8.5 (5.8–14.5)	4.1 (1.7–11.9)	NA	12.7 (7.7–18.7)	10.7 (6.9–18.0)	NA
Sex									
Female	309 (42.0)	119 (39.0)	.38	28 (45.9)	196 (45.5)	.68	22 (42.3)	56 (39.7)	.86
Day care attendance									
Yes	252 (34.3)	182 (60.0)	.028	39 (63.9)	311 (67.4)	.56	35 (67.3)	81 (57.5)	.31
Children in household									
1	181 (24.6)	101 (33.1)	.003[g]	13 (21.3)	97 (21.0)	.19[g]	15 (28.9)	51 (36.2)	.32[g]
2	349 (47.5)	143 (46.9)	.003[g]	25 (41.0)	238 (51.6)	.19[g]	28 (53.9)	58 (41.1)	.32[g]
≥3	204 (27.8)	59 (19.3)	.003[g]	23 (37.7)	126 (27.3)	.19[g]	9 (17.3)	30 (21.3)	.32[g]
Mean	2.1	2.0	<.001	2.3	2.2	.21	1.9	2.0	.75
Adults in household									
1	20 (2.7)	2 (0.6)	.06[g]	2 (3.3)	10 (2.2)	.06[g]	0 (0.0)	1 (0.7)	1.00[g]
2	685 (93.3)	293 (96.1)	.06[g]	54 (88.5)	438 (95.0)	.06[g]	51 (98.1)	134 (95.0)	1.00[g]
≥3	29 (3.9)	8 (2.6)	.06[g]	5 (8.2)	13 (2.8)	.06[g]	1 (1.9)	4 (2.8)	1.00[g]
Gestational age at birth (wk)									
Premature (<37 wk)	107 (14.6)	31 (10.1)	.06	13 (21.3)	57 (12.4)	.07	5 (9.6)	16 (11.4)	1.00
Term (≥37 wk)	627 (85.4)	274 (89.8)	.13[g]	48 (78.7)	401 (87.0)	.002[g]	46 (88.5)	121 (85.8)	.48[g]
33–36	77 (10.5)	23 (7.5)	.13[g]	6 (9.8)	46 (10)	.002[g]	5 (9.6)	11 (7.8)	.48[g]
29–32	23 (3.1)	8 (2.6)	.13[g]	7 (11.5)	7 (1.5)	.002[g]	0 (0.0)	5 (3.6)	.48[g]
<29	7 (0.9)	0 (0.0)	.13[g]	0 (0)	4 (0.9)	.002[g]	0 (0.0)	0 (0.0)	.48[g]
Mean ± SD	38.3 ± 2.5	38.7 ± 2.2	.007	37.5 ± 3.0	38.5 ± 2.2	.015	38.8 ± 1.7	38.6 ± 2.4	.89
Median (IQR)	39 (38–40)	39 (38–40)	NA	38 (37–40)	39 (38–40)	NA	39 (38–40)	39 (38–40)	NA
Birth weight (g)									
Any LBW (<2500)	98 (13.3)	25 (8.2)	.020	12 (19.7)	52 (11.3)	.09	4 (7.7)	15 (10.6	.60
≥2500	630 (85.8)	275 (90.2)	.12[g]	50 (80.7)	403 (88.6)	.044[g]	48 (92.3)	123 (87.2)	.60[g]
1500–2499	73 (9.9)	18 (5.9)	.12[g]	7 (11.3)	41 (8.9)	.044[g]	3 (5.8)	11 (7.8)	.60[g]
1000–1499	10 (1.3)	4 (1.3)	.12[g]	1 (1.6)	5 (1.1)	.044[g]	1 (1.9)	1 (0.7)	.60[g]
<1000	15 (2.0)	3 (1.0)	.12[g]	4 (6.5)	6 (1.3)	.044[g]	0 (0.0)	3 (2.1)	.60[g]
Mean ± SD	3173 ± 697	3324 ± 657	.005	3012 ± 791	3226 ± 656	.09	3329 ± 598	3318 ± 735	.99
Median (IQR)	3214 (2772–3642)	3325 (3027–3677)	NA	3196 (2718–3633)	3221 (2786–3642)	NA	3380 (3040–3677)	3381 (2972–3720)	NA

Table 2 continued.

Characteristic	Total, Hospital (n = 734)	Total, Clinic (n = 305)	P[a]	hMPV,[b] Hospital (n = 62)	RSV,[b] Hospital (n = 460)	P[c]	hMPV,[b] Clinic (n = 52)	RSV,[b] Clinic (n = 141)	P[d]
Underlying comorbidity									
Any	121 (16.5)	25 (8.2)	<.001	10 (16.4)	63 (13.7)	.56	3 (5.8)	11 (7.8)	.76
Pulmonary disease	38 (5.2)	4 (1.3)	.003	1 (1.6)	17 (3.7)	.71	1 (1.9)	2 (1.4)	1.00
Heart disease	29 (3.9)	4 (1.3)	.031	7 (11.5)	12 (2.6)	.003	0 (0.0)	1 (0.7)	1.00
Renal disease	11 (1.5)	3 (1.0)	.76	1 (1.6)	6 (1.3)	.58	0 (0.0)	1 (0.7)	1.00
Anemia	4 (0.5)	2 (0.6)	1.00	0 (0.0)	2 (0.4)	1.00	1 (1.9)	0 (0.0)	.26
Seizure disorder	22 (3.0)	4 (1.3)	.13	1 (1.6)	11 (2.4)	.78	0 (0.0)	0 (0.0)	NA
Trouble swallowing	6 (0.8)	0 (0.0)	.19	0 (0.0)	2 (0.4)	1.00	0 (0.0)	0 (0.0)	NA
Diabetes	7 (0.9)	1 (0.3)	.44	0 (0.0)	3 (0.65)	1.00	0 (0.0)	1 (0.7)	1.00
Other	42 (5.7)	9 (2.9)	.06	3 (4.9)	23 (5.0)	1.00	1 (1.9)	6 (4.2)	.67
No known predisposing condition[e]	514 (70.0)	250 (82.0)	<.001	39 (62.9)	340 (73.9)	.094	44 (84.6)	113 (80.1)	.53
Palivizumab RSV immunoprophylaxis during that winter season									
Yes	30 (4.1)	7 (2.3)	.19	7 (11.3)	9 (2.0)	.001	0 (0.0)	3 (2.1)	.56
2009 A/H1N1 immunization (among patients aged ≥6 mo)[f]									
Yes	60/82 (73.2)	42/61 (69.0)	.58	3/5 (60.0)	35/46 (76.1)	.59	9 (56.2)	26 (78.8)	.17
Seasonal influenza immunization (among patients aged ≥6 mo)									
Yes	174/355 (49.0)	118/240 (49.1)	1.00	14/43 (32.5)	100/190 (52.6)	.018	21 /45 (46.7)	61/109 (56.0)	.37
≥1 smoker in household									
Yes	78 (10.6)	8 (2.6)	<.001	5 (8.2)	45 (9.8)	.82	3 (5.8)	2 (1.4)	.12
Influenza immunization of household contacts									
None	357 (48.6)	125 (41.0)	.044[g]	33 (54.0)	213 (46.2)	.69[g]	20 (38.5)	57 (40.4)	.70[g]
Some	185 (25.2)	97 (31.8)	.044[g]	15 (24.6)	129 (28.0)	.69[g]	14 (26.9)	44 (31.2)	.70[g]
All	192 (26.1)	83 (27.2)	.044[g]	13 (21.3)	129 (28.0)	.69[g]	18 (34.6)	40 (28.4)	.70[g]
History of breast-feeding									
Yes	537 (73.1)	247 (81.0)	.002	45 (73.8)	341 (74.0)	1.00	13 (25.0)	25 (17.7)	.31

Data are no. or proportion (%) of patients, unless otherwise indicated. Missing values represent ≤2% of each variable and are therefore not presented.

Abbreviations: hMPV, human metapneumovirus; IQR, interquartile range; LBW, low birth weight; NA, not applicable; RSV, respiratory syncytial virus.

[a] Comparison of total hospitalized patients vs total clinic patients.

[b] Patients with hMPV-RSV coinfection were excluded from this analysis.

[c] Comparison of hMPV-infected hospitalized patients vs RSV-infected hospitalized patients.

[d] Comparison of hMPV-infected clinic patients vs RSV-infected clinic patients.

[e] No known predisposing condition is the absence of any of the following: chronic underlying comorbidity, prematurity, or LBW.

[f] For the 2009–2010 season only.

[g] Global P value of χ^2 test comparing multiple proportions.

(48.2%), respectively (Table 1). In both settings, hMPV was the second most important etiologic agent. In contrast to RSV, hMPV was identified more frequently in clinic patients, compared with hospitalized children (58 of 305 [19.0%] vs 69 of 734 [9.4%]; $P < .0001$). A respiratory virus was identified in 86.1% of hospital and 90.1% of clinic samples. Viral coinfection, defined as the presence of >1 virus in a specimen, was twice as frequent in the clinic setting (22.9% vs 11.7%; $P < .0001$). This difference was largely driven by adenoviruses, of which a very high proportion of clinic cases (39 of 49 [79.6%]) were coinfections.

Demographic and Clinical Characteristics

In the clinic, baseline characteristics for hMPV and RSV patients were similar (Table 2). Among hospitalized children, age distribution differed between viruses ($P < .0001$); the peak proportion of cases occurred at ages 6–11 months for hMPV (37.7%) and at ages 0–5 months for RSV (58.6%). Mean age was also higher for hMPV (10.5 vs 8.0 months; $P = .0008$). While the proportion of children who were born prematurely was not significantly different between hMPV and RSV hospitalizations, the distributions of gestational age (GA) at birth differed ($P = .002$), mainly because of more hMPV cases born at 29–32 weeks GA (11.5% vs 1.5%). Regarding chronic comorbidities, the only distinction between groups was that heart disease was more frequent among hMPV hospitalizations (11.5% vs 2.6%; $P = .003$). The majority of patients hospitalized with either virus had no predisposing condition (ie, prematurity, low birth weight [LBW], or chronic comorbidity).

The clinical manifestations and medical management of pediatric clinic patients were remarkably similar for both viruses (Table 3). However, important differences were observed among hospitalized children. Fever was more frequently reported in hMPV-infected subjects (91.9% vs 70.0%; $P < .001$), and their mean delay from symptom onset to presentation was shorter (3.1 vs 3.7 days; $P = .007$). A greater proportion of RSV infections (84.6%) were diagnosed as bronchiolitis, compared with hMPV infections (56.4%; $P < .001$), and RSV patients more frequently presented increased work of breathing (93.7% vs 83.9%; $P = .016$). High proportions of patients hospitalized with either virus (approximately 70%) received antibiotics. Regarding measures of disease severity, hospitalized RSV cases were more likely to require ≥30% oxygen (76.5% vs 62.9%; $P = .028$) and had longer mean duration of oxygen therapy (2.7 vs 2.1 days; $P = .042$) and hospital stay (3.73 vs 3.08 days; $P < .001$). Only 3 hMPV cases (4.8%) had a severity score of ≥2, compared with 18.0% for RSV ($P = .006$). PICU admission proportions were similar for hMPV (3.2%) and RSV (5.2%) hospitalizations. In multivariate analysis adjusting for age and prematurity (<37 weeks GA), RSV hospitalizations tended to more frequently require supplemental oxygen (RR, 1.20; 95% CI, .98–1.46) and had a higher risk of hospitalization >5 days (RR, 2.79; 95% CI, 1.07–7.30) or of manifesting a severity score ≥2 (RR, 4.04; 95% CI, 1.32–12.31).

Disease Severity Risk Factors

Univariate Analyses

Among hMPV-infected children, age 0–5 months, prematurity (GA <37 weeks), LBW, cardiac disease, and ≥3 children in the household were more frequent among hospitalized subjects, whereas day care exposure was associated with presentation to the pediatric clinic (Table 4). Risk factors for severe illness (severity score ≥1) in hospitalized cases included female sex, prematurity, LBW, and ≥3 children in the household; day care exposure was protective. Variables associated with hospitalization for RSV were age 0–5 months and ≥1 smoker in the household; day care exposure, a history of breast-feeding, and viral coinfection were more frequent among clinic patients. Among RSV hospitalizations, children aged 0–5 months and those with a history of prematurity or LBW were at higher risk for severe disease (severity score ≥2), whereas day care exposure was protective.

Multivariable Models

LBW and prematurity were highly associated with each other (Table 5). Consequently, we could not fit both into a model; a priori, we chose to include prematurity. The effect of day care exposure was strongly confounded by age for both viruses (only 4.2%–6.9% of children aged 0–5 months were exposed to day care, compared with 93.2%–96.0% of children aged 18–35 months); it lost significance in multivariable models and was not included.

Age <6 months (OR, 2.66; 95% CI, 1.04–6.81) and ≥3 children in the household (OR, 2.86; 95% CI, 1.17–6.98) were associated with hMPV hospitalization. In a separate model for severe disease (severity score ≥1) among hospitalized hMPV cases, prematurity (OR, 13.97; 95% CI, 1.50–130.0), female sex (OR, 4.32; 95% CI, 1.26–14.85), and genotype B infection (OR, 4.34; 95% CI, 1.27–14.88) were significant risk factors.

Regarding multivariable models for RSV disease severity, age 0–5 months (OR, 4.63; 95% CI, 2.94–7.28), ≥3 children in the household (OR, 1.93; 95% CI, 1.24–3.00), and the presence of an underlying comorbidity (OR, 1.99; 95% CI, 1.00–3.93) were associated with hospitalization, whereas a history of breast-feeding (OR, 0.55; 95% CI, .33–0.92) and viral coinfection (OR, 0.48; 95% CI, .30–0.78) were associated with attending the pediatric clinic. Prematurity (OR, 3.08; 95% CI, 1.63–5.83) and age 0–5 months (OR, 2.26; 95% CI, 1.31–3.89) were independent risk factors for severe RSV disease (severity score ≥2) among hospitalized children.

DISCUSSION

In our 4-year cohort of community and hospitalized cases aged 0–35 months, hMPV was second only to RSV as a cause of RTI and was responsible for approximately 10% of serious illnesses requiring hospital admission. Earlier studies

Table 3. Univariate Analysis of the Clinical Manifestations, Medical Management, and Disease Severity of Human Metapneumovirus (hMPV) Respiratory Tract Infection (RTI), Compared With Respiratory Syncytial Virus (RSV) RTI, Among Patients in the Hospital or Clinic

Clinical Manifestation	hMPV,[a] Hospital (n = 62)	RSV,[a] Hospital (n = 460)	P[b]	hMPV,[a] Clinic (n = 52)	RSV,[a] Clinic (n = 141)	P[c]
Symptom or sign						
Fever/chills	57 (91.9)	322 (70.0)	<.001	37 (71.2)	102 (72.3)	.85
Cough	62 (100.0)	453 (98.5)	1.00	50 (96.2)	139 (98.6)	.29
Increased work of breathing	52 (83.9)	431 (93.7)	.016	15 (28.9)	38 (27.0)	.85
Wheezing	55 (88.7)	424 (92.2)	.34	33 (63.5)	94 (66.7)	.73
Otalgia	18 (29.0)	88 (19.1)	.09	21 (40.4)	40 (28.4)	.11
Rhinorrhea	50 (80.6)	348 (75.6)	.43	51 (98.1)	140 (99.3)	.46
Sore throat	16 (25.8)	160 (34.8)	.19	16 (30.8)	54 (38.8)	.39
Hoarse voice	35 (56.4)	309 (67.2)	.12	16 (30.8)	31 (22.0)	.25
Lethargy	49 (79.0)	356 (77.4)	.87	39 (75.0)	97 (68.8)	.47
Loss of appetite	53 (85.4)	385 (83.7)	.85	39 (75.0)	117 (83.0)	.22
Vomiting	26 (41.9)	227 (49.3)	.28	11 (21.2)	25 (17.7)	.67
Diarrhea	18 (29.0)	132 (28.7)	1.00	10 (19.2)	15 (10.6)	.14
Apnea	9 (14.5)	64 (13.9)	.85	0 (0.0)	1 (0.7)	1.00
Convulsions	3 (4.8)	7 (1.5)	.10	1 (1.9)	1 (0.7)	.46
Delay from symptom onset to presentation (d)						
Mean ± SD	3.1 ± 3.3	3.7 ± 2.9	.007	…	…	
Median (IQR)	2.0 (1–3)	3.0 (2–4)	NA	…	…	
Duration of illness (d)						
Mean ± SD	13.3 ± 7.3	14.2 ± 7.7	.31	12.3 ± 6.7	13.3 ± 8.2	.69
Median (IQR)	11.5 (8–16)	12.0 (9–17)	NA	10.5 (8–15)	11.0 (8–16)	NA
Wheezing on auscultation	43 (69.3)	341 (74.1)	.44	30 (57.7)	84 (60.0)	.86
Rales on auscultation	40 (64.5)	318 (69.1)	.47	18 (34.6)	44 (31.2)	.72
Laboratory result						
Chest radiograph with infiltrate[d]	17/59 (28.8)	155/438 (35.4)	.38	4/6 (66.7)	2/11 (18.2)	.10
Positive blood culture[d]	1/40 (2.5)	2/253 (0.8)	.36	0/0 (0.0)	0/0 (0.0)	NA
Diagnosis[e]						
Bronchiolitis	35 (56.4)	389 (84.6)	<.001	30 (57.7)	78 (55.3)	.87
Pneumonia	18 (29.0)	159 (34.5)	.48	4 (7.7)	2 (1.4)	.046
Reactive airway disease exacerbation	10 (16.1)	41 (8.9)	.11	0 (0.0)	2 (1.4)	1.00
Otitis media	30 (48.4)	199 (43.3)	.49	12 (23.1)	29 (20.6)	.69
URTI	10 (16.1)	39 (8.5)	.06	21 (40.4)	58 (41.1)	1.00
Croup	1 (1.6)	3 (0.7)	.39	1 (1.9)	5 (3.6)	1.00
Pharyngitis	1 (1.6)	2 (0.4)	.32	2 (3.9)	1 (0.7)	.17
Sinusitis	1 (1.6)	0 (0.0)	.12	0 (0.0)	0 (0.0)	NA
Apnea	0 (0.0)	6 (1.3)	1.00	0 (0.0)	0 (0.0)	NA
Cystic fibrosis exacerbation	0 (0.0)	2 (0.4)	1.00	0 (0.0)	0 (0.0)	NA
Other	6 (9.7)	27 (5.9)	.26	0 (0.0)	0 (0.0)	NA
Management						
Antibiotics	44 (70.9)	314 (68.3)	.77	14 (26.9)	29 (20.6)	.34
Antivirals	0 (0.0)	2 (0.4)	1.00	0 (0.0)	1 (0.7)	1.00
Bronchodilators	46 (74.2)	345 (75.0)	.88	17 (32.7)	50 (35.5)	.87
Corticosteroids, inhaled	22 (35.5)	121 (26.3)	.13	10 (19.2)	26 (18.4)	1.00
Corticosteroids, systemic	16 (25.8)	89 (19.3)	.24	0 (0.0)	2 (1.4)	1.00
Consulted physician in following month	15 (25.9)	108 (24.9)	.87	25 (48.1)	50 (35.5)	.13
Supplemental oxygen required ($FiO_2 \geq 0.3$)	39 (62.9)	352 (76.5)	.028	NA	NA	NA
Duration of O_2 therapy (d), mean ± SD	2.1 ± 1.6	2.7 ± 1.9	.042	NA	NA	NA
Admission to PICU	2 (3.2)	24 (5.2)	.76	NA	NA	NA
Hospitalization duration (d)						
>5	4 (6.4)	75 (16.3)	.057	NA	NA	NA

Table 3 continued.

Clinical Manifestation	hMPV,[a] Hospital (n = 62)	RSV,[a] Hospital (n = 460)	P[b]	hMPV,[a] Clinic (n = 52)	RSV,[a] Clinic (n = 141)	P[c]
Mean ± SD	3.08 ± 3.03	3.73 ± 2.37	<.001	NA	NA	NA
Median (IQR)	2.0 (1–3)	3.00 (2–5)	NA	NA	NA	NA
Severity score[f]						
0	22 (35.5)	104 (22.6)	.003[g]	NA	NA	NA
1	37 (59.7)	273 (59.3)	.003[g]	NA	NA	NA
2	1 (1.6)	71 (15.4)	.003[g]	NA	NA	NA
3	2 (3.2)	12 (2.6)	.003[g]	NA	NA	NA
≥1	40 (64.5)	356 (77.4)	.038	NA	NA	NA
≥2	3 (4.8)	83 (18.0)	.006	NA	NA	NA

Data are no. or proportion (%) of patients, unless otherwise indicated. Missing values represent ≤2% of each variable and are therefore not presented.

Abbreviations: FiO_2, fraction of inhaled oxygen; IQR, interquartile range; NA, not applicable; PICU, pediatric intensive care unit; URTI, upper respiratory tract infection.

[a] Patients with hMPV-RSV coinfection were excluded from this analysis.

[b] Comparison of hMPV-infected hospitalized patients vs RSV-infected hospitalized patients.

[c] Comparison of hMPV-infected clinic patients vs RSV-infected clinic patients.

[d] Among patients who underwent that diagnostic test.

[e] Total does not equal 100% as >1 discharge diagnosis was allowed.

[f] Patients were attributed 1 point for the presence of each of the following criteria: admission to PICU, duration of hospitalization >5 days, and requirement for supplemental oxygen therapy ($FiO_2 \geq 0.3$).

[g] Global P value of χ^2 test comparing multiple proportions.

describing hMPV epidemiology and clinical characteristics have established that it is a major cause of pediatric pneumonia and bronchiolitis [2, 17, 18, 21]. Despite this significant burden, little is known about which patients are at highest risk of severe hMPV illness. Previous reports have been limited to retrospective analyses and/or have not controlled for confounding factors [22–24]. To our knowledge, this study is the first to prospectively evaluate host, environmental, and viral characteristics as independent risk factors for severe hMPV disease in young children, with the aim of identifying high-risk groups that would benefit most from preventive and therapeutic strategies. Young age, prematurity, female sex, household crowding, and genotype were identified as significant determinants of hMPV severity.

We observed that previously established patient risk factors for severe RSV disease, such as prematurity and young age, were also applicable to hMPV [6, 10, 25]. Age <6 months was associated with hMPV hospitalization, and prematurity was associated with severe disease among those hospitalized. However, prematurity was not a risk factor for RSV hospitalization in our model. Palivizumab prophylaxis among children with a history of prematurity may have masked some of its effect. It should also be noted that, in Quebec, children with complex medical histories (including prematurity) are referred to pediatricians for outpatient care. Consequently, the proportion of children born prematurely among our pediatric clinic patients (10.1%) was higher than that of the Quebec population (7.3%) [26]. Furthermore, despite systematic training and recruitment reminders, clinic physicians may have preferentially approached patients they considered at risk, such as those with a history of prematurity or comorbidities. This could lead to selection bias negatively affecting our ability to identify such high-risk conditions as being associated with hospitalization.

We found that female sex was associated with a severity score ≥1 in hospitalized hMPV cases. This was unexpected, as infant males are thought to have decreased pulmonary function, compared with females [27]. In particular, males born prematurely may be at higher risk of RSV hospitalization [28]. However, consistent with recent studies [6, 25], we did not observe an influence of sex on RSV severity overall. According to our findings, it is therefore possible that the effect of sex on clinical illness may differ between respiratory viruses, underscoring the need to characterize determinants of disease severity specifically for hMPV, despite its many similarities to RSV.

Studies assessing environmental factors, including those that increase the likelihood of early primary RSV infection (eg, multiple siblings and day care exposure) or affect lung function (eg, passive exposure to tobacco smoke) have produced conflicting results [2, 10]. Environmental variables may be particularly susceptible to confounding, as evidenced by the large influence exerted by covariates on the effect of day care exposure, which appeared protective in our univariate analyses largely because of the higher age of exposed patients. Furthermore, it is difficult to exclude residual confounding

Table 4. Univariate Analyses of Host, Environmental, and Virological Risk Factors for Disease Severity Among Children in the Hospital or Clinic With Human Metapneumovirus (hMPV) Respiratory Tract Infection (RTI) or Respiratory Syncytial Virus (RSV) RTI

	RSV, No. (%) (n = 614)					hMPV, No. (%) (n = 127)			
		Hospital, by Severity Score[a]					Hospital, by Severity Score[a]		
Factor	Clinic (n = 147)	0 (n = 105)	≥1 (n = 362)	≥2 (n = 83)	Overall (n = 467)	Clinic (n= 58)	0 (n = 23)	≥1 (n = 46)	Overall (n = 69)
Host									
Age (mo)									
<6	31 (21.1)	52 (49.5)	221 (61.0)	**60 (72.3)**[b]	**273 (58.5)**[c]	8 (13.8)	8 (34.8)	13 (28.3)	**21 (30.4)**[c]
6–11	48 (32.7)	23 (21.9)	56 (15.5)	12 (14.5)	79 (16.9)	20 (34.5)	5 (21.7)	21 (45.7)	26 (37.7)
12–17	32 (21.8)	11 (10.5)	39 (10.8)	5 (6.0)	50 (10.7)	14 (24.1)	5 (21.7)	8 (17.4)	13 (18.8)
18–36 (ref)	36 (24.5)	19 (18.1)	46 (12.7)	6 (7.2)	65 (13.9)	16 (27.6)	5 (21.7)	4 (8.7)	9 (13.0)
Sex									
Female	60 (40.8)	47 (44.8)	152 (42.0)	38 (45.8)	199 (42.6)	26 (44.8)	6 (26.1)	**26 (56.5)**[d]	32 (46.4)
Gestational age at birth (wk)									
<29	0 (0.0)	0 (0.0)	4 (1.1)	0 (0.0)	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
29–32	5 (3.4)	0 (0.0)	7 (1.9)	**3 (3.6)**[b]	7 (1.5)	0 (0.0)	0 (0.0)	**7 (15.2)**[d]	**7 (10.1)**[c]
33–36	11 (7.5)	12 (11.4)	35 (9.7)	**14 (16.9)**[b]	47 (10.1)	5 (8.6)	1 (4.4)	6 (14.6)	7 (10.1)
≤37 (premature)	16 (10.9)	12 (11.4)	46 (12.7)	**19 (22.9)**[b]	58 (12.4)	5 (8.6)	1 (4.3)	**13 (28.3)**[d]	**14 (20.3)**[c]
≥37 (term; ref)	127 (86.4)	91 (86.7)	315 (87.0)	64 (77.1)	406 (86.9)	52 (89.7)	22 (95.7)	33 (71.7)	55 (79.7)
Birth weight (g)									
<1000	3 (2.0)	0 (0.0)	6 (1.7)	2 (2.4)	6 (1.3)	0 (0.0)	0 (0.0)	**4 (8.7)**[d]	**4 (5.8)**[c]
1000–1499	1 (0.7)	1 (1.0)	4 (1.1)	0 (0.0)	5 (1.1)	1 (1.7)	0 (0.0)	1 (2.2)	1 (1.5)
1500–2499	11 (7.5)	10 (9.5)	32 (8.8)	**14 (16.9)**[b]	42 (9.0)	3 (5.2)	1 (4.3)	**7 (15.2)**[d]	8 (11.6)
<2500 (LBW)	15 (10.2)	11 (10.5)	42 (11.6)	**16 (19.3)**[b]	53 (11.3)	4 (6.9)	1 (4.3)	12 (26.1)	**13 (18.8)**[c]
≥2500 (ref)	130 (88.4)	93 (88.6)	316 (87.3)	67 (80.7)	409 (87.6)	54 (93.1)	22 (95.7)	34 (73.9)	56 (81.2)
Comorbidity									
Any	12 (8.2)	14 (13.3)	49 (13.5)	11 (13.3)	63 (13.5)	4 (6.9)	4 (17.4)	7 (15.2)	11 (15.9)
Pulmonary disease	2 (1.4)	3 (2.9)	14 (3.9)	1 (1.2)	17 (3.6)	1 (1.7)	0 (0.0)	1 (2.2)	1 (1.5)
Heart disease	1 (0.7)	1 (1.0)	10 (2.8)	3 (3.6)	11 (2.4)	0 (0.0)	3 (13.0)	4 (8.7)	**7 (10.1)**[a]
Kidney	2 (1.4)	0 (0.0)	5 (1.4)	1 (1.2)	5 (1.1)	1 (1.7)	1 (4.4)	0 (0.0)	1 (1.4)
Anemia	0 (0.0)	1 (1.0)	1 (0.3)	0 (0.0)	2 (0.4)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
CNS disorders, including seizures	0 (0.0)	2 (1.9)	9 (2.5)	1 (1.2)	11 (2.4)	0 (0.0)	0 (0.0)	1 (2.2)	1 (1.4)
Swallowing difficulties	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes/metabolic disorders	1 (0.7)	2 (1.9)	1 (0.3)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	6 (4.1)	5 (4.8)	19 (5.2)	5 (6.0)	24 (5.1)	1 (1.7)	1 (4.3)	4 (8.7)	5 (7.2)
Environmental									
Day care attendance	85 (57.8)	42 (40.0)	111 (30.7)	**15 (18.1)**[b]	**153 (32.8)**[c]	39 (67.2)	13 (56.5)	**14 (30.4)**[d]	**27 (39.1)**[c]
≥3 children in household	30 (20.4)	30 (28.6)	100 (27.6)	22 (26.5)	130 (27.8)	9 (15.5)	4 (17.4)	**23 (50.0)**[d]	**27 (39.1)**[c]
≥1 smoker in household	2 (1.4)	7 (6.7)	39 (10.8)	11 (13.3)	**46 (9.8)**[c]	3 (5.2)	0 (0.0)	6 (13.0)	6 (8.7)
History of breast-feeding	119 (81.0)	79 (75.2)	266 (73.5)	63 (75.9)	**345 (73.9)**[c]	45 (77.6)	8 (34.8)	11 (23.9)	50 (72.5)
Virological									
Viral coinfection[e]	43 (29.3)	16 (15.2)	50 (13.8)	7 (8.4)	**66 (14.1)**[a]	20 (34.5)	5 (21.7)	12 (26.1)	17 (24.6)
Genotype B	64 (43.5)	61 (58.1)	153 (42.3)	40 (48.2)	214 (45.8)	31 (53.4)	8 (34.8)	26 (56.5)	34 (49.3)

Statistically significant comparisons are in bold. Missing values represent ≤2% of each variable and are therefore not presented.

Abbreviations: CNS, central nervous system; LBW, low birth weight; ref, reference category when calculating the relative risk of other categories within that variable.

[a] Hospitalized patients were attributed 1 point for the presence of each of the following outcomes: admission to pediatric intensive care unit, duration of hospitalization >5 days, and requirement of oxygen therapy (fraction of inhaled $O_2 \geq 0.3$).

[b] Statistically significant when comparing RSV-infected hospitalized children with a severity score ≥2 to those with a severity score <2.

[c] Statistically significant when comparing hospitalized children to pediatric clinic outpatients.

[d] Statistically significant when comparing hMPV-infected hospitalized children with a severity score ≥1 to those with a severity score <1.

[e] Patients who tested positive for hMPV or RSV and ≥1 other respiratory virus by multiplex polymerase chain reaction/DNA microarray assay.

Table 5. Multivariate Logistic Regression Models for Risk Factors of Severe Human Metapneumovirus (hMPV) Respiratory Tract Infection (RTI) or Respiratory Syncytial Virus (RSV) RTI Among Children in the Hospital or Clinic

	Adjusted OR (95% CI)			
Risk Factor	hMPV, Hospital vs Clinic	hMPV, Severe Disease, Hospital (Severity Score ≥1)[a]	RSV, Hospital vs Clinic	RSV, Severe Disease, Hospital (Severity Score ≥2)[a]
Age <6 mo	**2.66 (1.04–6.81)**	…	**4.63 (2.94–7.28)**	**2.26 (1.31–3.89)**
Age <12 mo	…	1.81 (0.51–6.45)	…	…
≥3 children in the household	**2.86 (1.17–6.98)**	…	**1.93 (1.24–3.00)**	…
Prematurity (<37 wk GA)	2.31 (0.73–7.30)	**13.97 (1.50–130.0)**	1.29 (0.68–2.43)	**3.08 (1.63–5.83)**
Female sex	…	**4.32 (1.26–14.85)**	…	…
Genotype B infection	…	**4.34 (1.27–14.88)**	…	…
Presence of a comorbidity	…	…	**1.99 (1.00–3.93)**	…
History of breast-feeding	…	…	**0.55 (0.33–0.92)**	…
Viral coinfection	…	…	**0.48 (0.30–0.78)**	0.58 (0.25–1.35)

Statistically significant ORs are in bold. Cells with ellipses denote that the associated variable was not retained in that model.

Abbreviations: CI, confidence interval; GA, gestational age; OR, odds ratio.

[a] Patients were attributed 1 point for the presence of each of the following criteria: admission to the pediatric intensive care unit, duration of hospitalization >5 days, requirement for supplemental oxygen therapy (fraction of inhaled $O_2 \geq 0.3$).

due to other unmeasured (eg, socioeconomic status) or unknown variables. Nonetheless, consistent with American and Canadian RSV immunoprophylaxis guidelines that consider the presence of preschool-aged siblings [11] and household crowding [12] to be risk factors, we observed that ≥3 children in the household was independently associated with hospitalization in both hMPV and RSV RTI.

Virulence differences between viral genotypes, whether related to replication capacity or glycoprotein-triggered immunopathology, may have important implications for vaccine development [10]. We observed that hMPV genotype B produced more severe illness among hospitalized children. However, previous studies reported opposite [22] or null findings [23] in unadjusted analyses; the effect of RSV genotype is also controversial [10]. Variations in pathogenicity of specific strains [29] or sublineages [13] within genotypes of paramyxoviruses may cause these seemingly conflicting results and need to be further assessed.

With sensitive multiplex molecular diagnostic methods, the detection of >1 virus in a pediatric respiratory sample is frequent [20]. Although experimental models have yet to address this issue, the question of a cumulative pathogenic effect in bronchiolitis has been raised, particularly for RSV-hMPV coinfections [24]. Our results do not support such a hypothesis. RSV-hMPV coinfections were not frequent enough for meaningful subgroup analyses; however, none had a severity score ≥2. Furthermore, RSV coinfections were inversely associated with hospitalization. Recently, others have also reported lower severity of RSV coinfections specifically [30] and viral coinfections overall [31]. Because detection of viral RNA/DNA may sometimes represent carryover from a previous RTI, the apparent protective effect of coinfection could be related to antiviral immune responses (eg, interferon induction) to recent infection. Interestingly, the most frequent RSV coinfecting agent in our cohort was adenovirus, a virus prone to prolonged low-level shedding [31].

Finally, RSV infections themselves may be more aggressive than infections with other viruses. Garcia et al recently demonstrated that RSV bronchiolitis was independently associated with severe outcomes, compared with non-RSV bronchiolitis [25]. Similarly, we found that children hospitalized for RSV RTI were 4 times as likely to have a severity score of ≥2, compared with children hospitalized for hMPV RTI.

There are several potential limitations to our study. First, we identified hospitalized cases on the basis of collection of NPAs for clinical diagnostic purposes. For that reason, we were not able to identify RTI unrecognized by treating physicians because of atypical manifestations. Specifically, influenza may present in young children with systemic symptoms and few or no respiratory findings; therefore, we may have underestimated its frequency. Also, we did not systematically assess the potential influence of bacterial copathogens on disease severity. Experimental animal data suggest that prior infection with hMPV predisposes to severe pneumococcal pneumonia [32]. We did not test for bacteria in our participants' nasopharyngeal secretions (indicating colonization or possible infection), and it would not have been ethical to obtain lower respiratory tract specimens from young children solely for the purpose of our study. Furthermore, although we evaluated >1000 children with RTI, our ability to assess risk factors for hMPV disease severity was limited by the incidence of hMPV-associated hospitalization (69 cases). Consequently, we were unable to assess in multivariable models the effect of specific high-risk comorbidities associated with severity in univariate analyses, such as

cardiac disease or different degrees of prematurity. In addition, as discussed, a potential selection bias toward at-risk patients may have been present among pediatric clinic patients. The last 2 limitations should bias toward the null; yet, our results show significant associations between hypothesized risk factors and hMPV disease severity. Similarly to earlier evaluations of RSV [9, 28], multicenter studies will be necessary to characterize the role of specific comorbidities in hMPV illness, especially among premature infants. Finally, because very few (ie, 3) hMPV patients had a severity score of ≥2, we dichotomized our index as 0 and ≥1 to assess hMPV disease severity. This may not have allowed us to capture the risk factors associated with the most severe outcomes of hMPV RTI, such as PICU admission or death.

In summary, we present prospective data proposing host, environmental, and viral determinants of hMPV disease severity. Specifically, young age, prematurity, female sex, household crowding, and genotype were identified as independent risk factors for severe hMPV outcomes. Several, although not all, of these variables were also associated with RSV severity. These findings should serve as a basis for future studies and will inform hMPV prevention and treatment strategies when they become available.

Notes

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G. B. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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