

# Clinical Features of Human Metapneumovirus-Associated Community-acquired Pneumonia Hospitalizations

Leigh M. Howard,<sup>1</sup> Kathryn M. Edwards,<sup>1</sup> Yuwei Zhu,<sup>2</sup> Carlos G. Grijalva,<sup>3</sup> Wesley H. Self,<sup>4</sup> Seema Jain,<sup>5</sup> Krow Ampofo,<sup>6</sup> Andrew T. Pavia,<sup>6</sup> Sandra R. Arnold,<sup>7</sup> Jonathan A. McCullers,<sup>7,8</sup> Evan J. Anderson,<sup>9</sup> Richard G. Wunderink,<sup>10</sup> and Derek J. Williams<sup>1</sup>

<sup>1</sup>Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA, <sup>2</sup>Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA, <sup>3</sup>Department of Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee, USA, <sup>4</sup>Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA, <sup>5</sup>Centers for Disease Control and Prevention, Atlanta, Georgia, USA, <sup>6</sup>University of Utah Health Sciences Center, Salt Lake City, Utah, USA, <sup>7</sup>University of Tennessee Health Sciences Center, Memphis, Tennessee, USA, <sup>8</sup>St. Jude Children's Research Hospital, Memphis, Tennessee, USA, <sup>9</sup>Departments of Pediatrics and Medicine, Emory University School of Medicine, Atlanta, Georgia, USA, and <sup>10</sup>Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

(See the Editorial Commentary by Papenburg and Alghounaim on pages 118–20.)

**Background.** Human metapneumovirus (HMPV) is a leading cause of respiratory tract infections. Few studies have compared the clinical characteristics and severity of HMPV-associated pneumonia with other pathogens.

**Methods.** Active, population-based surveillance was previously conducted for radiographically confirmed, community-acquired pneumonia hospitalizations among children and adults in 8 United States hospitals. Clinical data and specimens for pathogen detection were systematically collected. We described clinical features of all HMPV-associated pneumonia and, after excluding codetections with other pathogen types, we compared features of HMPV-associated pneumonia with other viral, atypical, and bacterial pneumonia and modeled the severity (mild, moderate, and severe) and length of stay using multivariable proportional odds regression.

**Results.** HMPV was detected in 298/2358 (12.6%) children and 88/2320 (3.8%) adults hospitalized with pneumonia and was commonly codetected with other pathogens (125/298 [42%] children and 21/88 [24%] adults). Fever and cough were the most common presenting symptoms of HMPV-associated pneumonia and were also common symptoms of other pathogens. After excluding codetections in children ( $n = 1778$ ), compared to HMPV (reference), bacterial pneumonia exhibited increased severity (odds ratio [OR], 3.66; 95% confidence interval [CI], 1.43–9.40), respiratory syncytial virus (RSV; OR, 0.76; 95% CI, .59–.99) and atypical (OR, 0.39; 95% CI, .19–.81) infections exhibited decreased severity, and other viral pneumonia exhibited similar severity (OR, 0.88; 95% CI, .55–1.39). In adults ( $n = 2145$ ), bacterial (OR, 3.74; 95% CI, 1.87–7.47) and RSV pneumonia (OR, 1.82; 95% CI, 1.32–2.50) were more severe than HMPV (reference), but all other pathogens had similar severity.

**Conclusions.** Clinical features did not reliably distinguish HMPV-associated pneumonia from other pathogens. HMPV-associated pneumonia was less severe than bacterial and adult RSV pneumonia, but was otherwise as or more severe than other common pathogens.

**Keywords.** human metapneumovirus; community-acquired pneumonia; viral pneumonia.

Human metapneumovirus (HMPV) is an important cause of acute respiratory illness (ARI) across all ages [1–7], with manifestations ranging from a mild upper respiratory tract infection to a lower respiratory tract infection (LRTI), including croup, bronchiolitis, and pneumonia. Younger children and older adults are most likely to experience severe disease [1, 2, 5, 6, 8, 9]. Previous studies indicate that HMPV and respiratory syncytial virus (RSV) exhibit similar clinical manifestations and seasonality [10], and are leading viral causes of LRTI [11–15]. However, few studies directly compare clinical features and outcomes of HMPV with other pathogens in cases of radiographically confirmed community-acquired pneumonia (CAP) [16].

The Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) study was a prospective, multicenter, population-based, active surveillance study designed to determine the etiology of CAP in hospitalized children and adults [17, 18]. Systematic and prospective microbiological testing for respiratory pathogens was performed using multiple modalities, allowing for the detailed study of the clinical features and outcomes of HMPV-associated CAP across all ages. Our objectives were to determine the clinical features of HMPV pneumonia in children and adults, as compared with pneumonia caused by RSV, other viruses, atypical bacteria, and usual bacterial pathogens.

## METHODS

### Patient Enrollment and Data Collection

Children and adults were enrolled from January 2010 through June 2012 at 8 hospitals in Chicago, IL; Memphis, TN; Nashville, TN; and Salt Lake City, UT. Detailed study methods have been reported elsewhere [17, 18]. Briefly, patients were eligible if they

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Correspondence: L. M. Howard, CCC-5317 MCN, 1161 21<sup>st</sup> Ave South, Nashville, TN 37232 (leigh.howard@vumc.org).

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were admitted to a study hospital, resided in the study catchment area, had evidence of an acute infection (fever, chills, hypothermia, leukocytosis, or leukopenia), had evidence of an ARI, and had radiographic findings compatible with pneumonia that were confirmed by independent study radiologists. Patients were excluded if they were recently hospitalized, had enrolled within the previous 28 days, or had an alternative respiratory diagnosis, tracheostomy, cystic fibrosis, cancer, a recent organ or stem cell transplant, graft-versus-host disease or bronchiolitis obliterans, or a human immunodeficiency virus (HIV) infection with CD4 <200 cells/mm<sup>3</sup> or <14%. Children and adults residing in extended care facilities and unable to function independently were also excluded. Detailed demographic, epidemiologic, and clinical data were systematically collected. The study was approved by institutional review boards at each institution and by the CDC [17, 18].

### Sample Collection and Laboratory Testing

Sera, blood, and nasopharyngeal/oropharyngeal (NP/OP) swabs were obtained as soon as possible after enrollment. Convalescent sera were collected 3–10 weeks later, when possible. Pleural fluid (PF), endotracheal (ET) aspirates, or bronchoalveolar (BAL) specimens, if obtained for routine clinical care, were evaluated. In adults, urine was collected, and sputum was obtained in those patients with a productive cough. Only samples collected ≤72 hours after admission were included, except for PF (≤7 days after admission) [17, 18].

Blood, PF, sputum, ET, and BAL specimens were cultured using standard techniques. Bacterial real-time polymerase chain reaction (PCR) was performed on PF for all ages, and whole-blood *Streptococcus pneumoniae* and *Streptococcus pyogenes* PCR was performed for children. For adults, *Legionella pneumophila* and *S. pneumoniae* urine antigen testing was performed. *Legionella* PCR assays were performed on sputum, regardless of the sputum quality [18].

NP/OP swabs were tested by a CDC-developed PCR assay [19] for the detection of HMPV; adenovirus (AdV); coronaviruses (CoV) 229E, HKU1, NL63, and OC43; human rhinovirus (HRV); influenza A/B viruses; parainfluenza viruses (PIV) 1, 2, and 3; RSV; *Chlamydia pneumoniae*; and *Mycoplasma pneumoniae*. Serology for AdV, HMPV, influenza A/B, PIV, and RSV was performed on acute and convalescent sera [17, 18].

### Pneumonia Definitions

HMPV-associated pneumonia was defined as pneumonia with HMPV virus detection by NP/OP swab PCR and/or a ≥4-fold rise in antibody titers between acute and convalescent sera. RSV-associated pneumonia was defined similarly. All other patients with pneumonia were considered negative for HMPV and/or RSV.

Some patients with HMPV-associated or RSV-associated pneumonia also had codetections with other pathogens. HMPV-only and RSV-only pneumonia were defined as the

detection of only the single virus. Other viral pneumonia was defined as pneumonia with at least 1 other virus detected (AdV, CoV, influenza, HRV, or PIV, inclusive of codetections) by NP/OP swab PCR and/or a ≥4-fold rise in antibody titers between acute and convalescent sera without the codetection of HMPV, RSV, or bacteria [17, 18].

Bacterial pneumonia was defined as pneumonia with bacterial detection by blood, ET, BAL, PF culture, or PF PCR in any patient; bacterial detection by whole-blood PCR in children; or bacterial detection by urine antigen testing or sputum culture in adults [17, 18]. Patients in the “bacterial-only” category had only typical bacteria, such as *S. pneumoniae*, *Staphylococcus aureus*, and *S. pyogenes*, without atypical bacteria or any virus detected. Atypical bacterial pneumonia included detections of *C. pneumoniae*, *M. pneumoniae*, or *L. pneumophila* by NP/OP swab PCR or urine antigen without typical bacteria or viruses detected.

### Outcomes: Disease Severity and Length of Stay

For children and adults, illness severity was categorized in HMPV, RSV, and bacterial mutually exclusive groups according to the following hierarchy: (1) severe pneumonia, defined as an in-hospital death, need for extracorporeal membrane oxygenation, acute respiratory distress syndrome, shock, and/or invasive mechanical ventilatory support; (2) moderate pneumonia, defined as an intensive care unit (ICU) admission without meeting the criteria for severe pneumonia; and (3) mild pneumonia, defined as all other hospitalized patients that did not require ICU admission [20]. We defined length of stay (LOS) as the time from admission to hospital discharge.

### Statistical Analysis

Pediatric and adult analyses were performed separately and stratified by age group. We described patients with HMPV-associated pneumonia (any case in which HMPV was detected, including codetections with other pathogens). We compared features of HMPV-only pneumonia to those with RSV-only, other viral (sole or codetection of any combination of AdV, CoV, influenza, HRV, and/or PIV), bacterial-only, and atypical bacterial-only pneumonia, as well as pneumonia with no pathogens detected. Categories were mutually exclusive; viral-bacterial, viral-atypical, and atypical-bacterial codetections were excluded from these comparisons. Any viral codetection, including HMPV or RSV, was excluded. This analysis was limited to patients with at least 1 specimen available for both viral and bacterial pathogen detection, as previously described [17, 18]. Chi-square and Kruskal-Wallis tests were used to compare categorical and continuous variables, respectively, between and among groups, with *P* values ≤ .05 considered statistically significant. We performed a multivariable proportional odds regression to evaluate the association between the pneumonia

etiologic category (HMPV only [reference], RSV only, other viral, atypical bacterial, bacterial, or no pathogen detected) and clinical disease severity by the 3-level scale. We used a multivariable proportional hazards regression to evaluate the association between the etiologic category and LOS. Covariates for the regression models were selected a priori and included site, year, age, race, sex, insurance status, influenza and pneumococcal vaccination history, antibiotic use and symptom duration prior to admission, cigarette smoke exposure, and presence of comorbidities. For all subjects, comorbidities included chronic kidney or liver disease, neurologic disorder, diabetes mellitus, immunosuppression, HIV infection (CD4 count > 200/mm<sup>3</sup>), and splenectomy. Comorbidities in children also included asthma/reactive airway disease, chromosomal disorders, and preterm birth (<2 years). Adult comorbidities included chronic lung or heart disease. Clustering of observations at the hospital level was accounted for using the Huber-White method for variance calculations in the regression models. Analyses were conducted in Stata Version 14.2 (StataCorp LLC, College Station, TX) and R (version 3.5.0).

## RESULTS

### Epidemiological Features of Human Metapneumovirus–Associated Community-acquired Pneumonia

#### Children

Overall, HMPV was detected in 298/2358 (12.6%) children (median age, 23 months) with pneumonia. In 173/298 (58%) cases, HMPV was the sole pathogen detected. HMPV was most commonly codetected with other viruses (97/125; 78%), including RSV, AdV, and/or HRV [18]; bacterial pathogens (13/125; 10%); or both bacterial and viral pathogens (8/125; 6%). Peak HMPV detections occurred in the winter and spring (Figure 1A). For HMPV, among those with specimens available for both viral and bacterial testing (n = 285), 252 (88%) were detected by PCR, 108 (38%) by serology, and 75 (26%) by both modalities [18, 21].

#### Adults

Human metapneumovirus was detected in 88/2320 (3.8%) adults with pneumonia (median age, 56.5 years). HMPV-associated pneumonia cases were relatively well-distributed among adult age groups, with the exception of the group ≥80 years old, in which only 5/316 (1.6%) cases of HMPV-associated pneumonia occurred. Of 88 HMPV cases in adults, HMPV was the sole pathogen detected in 67 (76%) cases. HMPV was most commonly codetected with other viruses (10/21, 48%), including RSV and/or PIV [17], or bacterial pathogens (9/21, 43%). Seasonal detection patterns were similar to those in children (Figure 1B). For HMPV pneumonia, 63 (72%) were detected by PCR, 9 (10%) by serology, and 16 (18%) by both modalities [17, 21].

### Clinical Features of Human Metapneumovirus–Only Pneumonia Compared to Respiratory Syncytial Virus–Only Pneumonia

#### Children

When limited to children with samples tested for both viruses and bacteria, and after the exclusion of samples from children with the codetection of other pathogen types, 1778 pediatric pneumonia cases were analyzed. In unadjusted comparisons, children with HMPV pneumonia were older than children with RSV (Table 1). Children with HMPV pneumonia were significantly less likely to have a cough (96%), dyspnea (64%), retractions (42%), documented wheezing (39%), and a white blood cell count >15 × 10<sup>3</sup> (13%) than those with RSV pneumonia (99%, 77%, 53%, 51%, and 17%, respectively; *P* ≤ .05 for all comparisons). Of HMPV pneumonia cases, 24% were characterized as moderate or severe, compared to 20% in children with RSV (*P* = .501; Table 3).

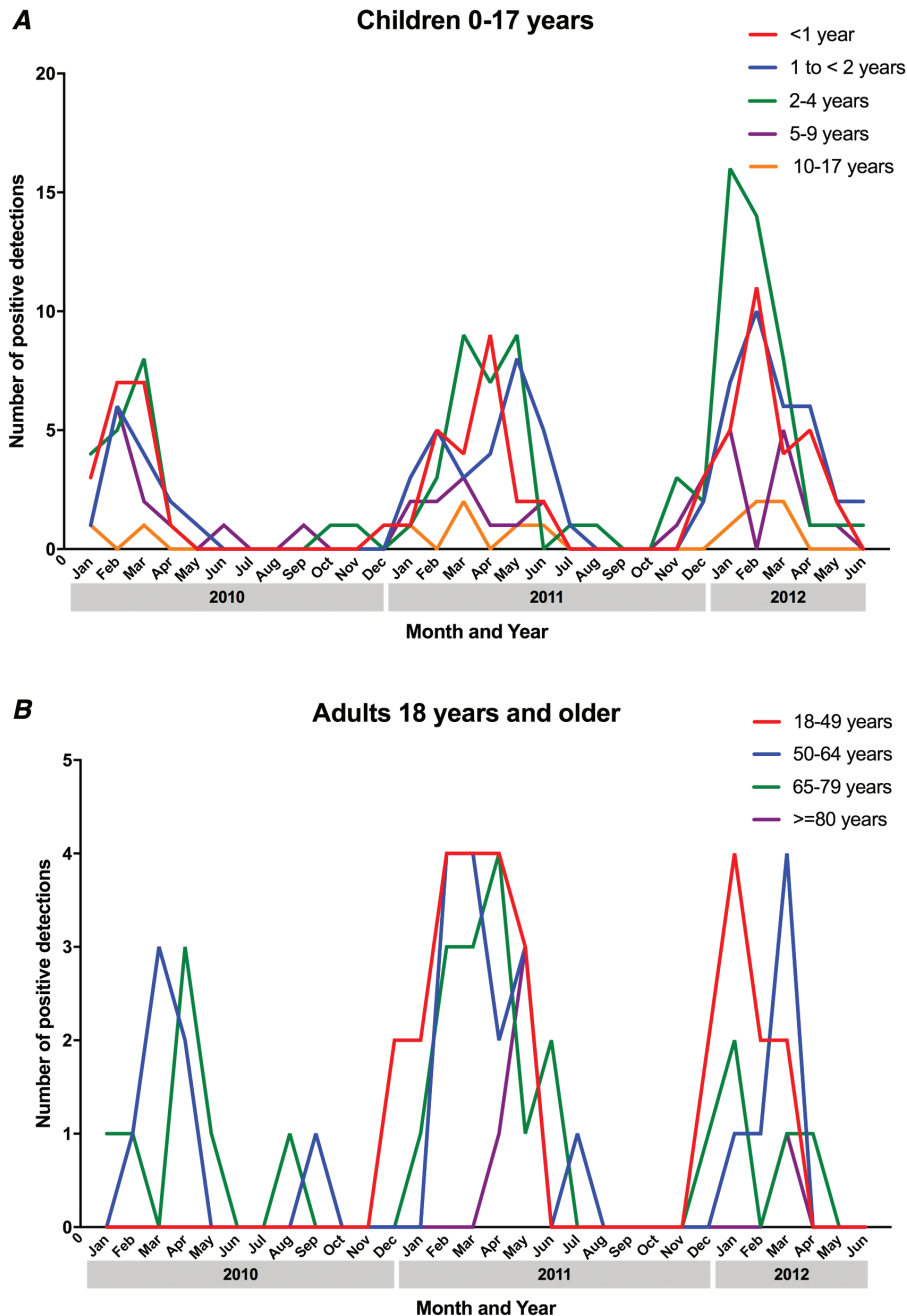
#### Adults

When limited to adults with samples tested for both viruses and bacteria, and after the exclusion of codetections with other pathogen types, 2145 pneumonia cases were analyzed. In adults, only 4% of HMPV pneumonia cases occurred in the ≥80 age group, while 20% of RSV infections occurred in adults ≥80 (*P* = .023; Table 2). The prevalences of cough, dyspnea, and documented wheezing did not differ significantly between adults with HMPV and RSV, but those with HMPV were less likely to exhibit rhinorrhea (43%) than those with RSV (62%; *P* = .042). Of adult HMPV pneumonia cases, 19% were characterized as moderate or severe, compared to 29% in adults with RSV (*P* = .108; Table 3).

### Clinical Features of Human Metapneumovirus–Only Pneumonia Compared to Other Viral and Bacterial Pathogens

#### Children

In unadjusted comparisons, among 1778 cases of pediatric pneumonia, excluding codetection with other pathogen types, children with HMPV-only pneumonia (165/1778; 9%) were younger (median 28 months) than children with other viral, atypical-only, and bacterial-only pneumonia (medians, 32, 104, and 55 months, respectively; Table 1) [18]. Gender also differed among pathogens, with HMPV exhibiting a slight female predominance. The proportion with an underlying comorbidity was higher in HMPV cases (47%) than in children with bacterial pneumonia (27%) and was similar to cases with other viral and atypical bacterial pneumonia (41–55%). Wheezing was more common in HMPV (39%) and other viral infections (49%) than in atypical bacterial (25%) or bacterial (12%) infections. The proportion of children requiring supplemental oxygen was highest in HMPV infections (123/165; 75%), and more common than in children with other viral, atypical bacterial, or bacterial infections (50–64%). Single or multi-lobe infiltrate patterns were seen on chest X-rays in 41% of HMPV infections, less commonly than in bacterial pneumonia cases



**Figure 1.** Detection of human metapneumovirus by month and year among US (A) children and (B) adults with community-acquired pneumonia requiring hospitalization.

(71%) and similar to in cases with other pathogen types (36–46%). Parapneumonic effusion was less common among children with HMPV (7%) and other viral (6%) infections than those with atypical bacterial (21%) or bacterial (66%) pneumonia. Pneumonia of moderate severity occurred in 18% of HMPV-only cases, slightly higher than the rates of pneumonia caused by bacteria (15%), other viruses (13%), and atypical bacteria (9%), while severe pneumonia occurred less commonly in HMPV (6%) and other types of pneumonia (1–8%) than in bacterial pneumonia cases (29%).

#### Adults

In unadjusted comparisons of pathogen types excluding codetection with other pathogens, HMPV was detected in 67/2145 (3.0%) adult patients with pneumonia. Females comprised the majority of HMPV (69%) pneumonia cases; gender was more equally distributed among other viral, atypical bacterial, and bacterial pneumonias (female, 43–54%; Table 2) [17]. The proportion with an underlying comorbidity in HMPV infections (81%) was similar to the rates in other viral (77%), and bacterial (83%) infections but more common than in atypical



**Table 1. Select Characteristics of Hospitalized Children with Human Metapneumovirus–Only Pneumonia Compared with Respiratory Syncytial Virus, Other Viral, Bacterial, and Atypical Pneumonia**

	HMPV-Only Pneumonia, n = 165, % (n)	RSV-Only Pneumonia, n = 358, % (n)	Other Viral Pneumonia, n = 665, % (n)	Atypical-Only Pneumonia, n = 133, % (n)	Bacterial-Only Pneumonia, n = 41, % (n)	No Pathogen Detected, n = 416, % (n)	P Value
Female sex	56% (92)	53% (190)	43% (284)	38% (51)	34% (14)	43% (178)	<.001 <sup>a</sup>
Median age, months (IQR)	28.0 (14.0–51.0)	17.0 (7.0–30.5)	32.0 (13.0–72.0)	104.0 (67.0–140.0)	55.0 (16.0–104.0)	57.5 (18.0–113.8)	<.001 <sup>a</sup>
Age group	...	***	...	...	...	...	<.001 <sup>a</sup>
<1 year	19% (31)	35% (125)	22% (144)	2% (2)	15% (6)	15% (62)	
1 to < 2 years	25% (41)	31% (110)	21% (138)	6% (8)	12% (5)	13% (56)	
2–4 years	37% (61)	28% (99)	26% (172)	14% (19)	29% (12)	22% (92)	
5–9 years	14% (23)	4% (13)	21% (141)	39% (52)	29% (12)	27% (113)	
10–17 years	5% (9)	3% (11)	11% (70)	39% (52)	15% (6)	22% (93)	
Race/ethnicity	...	...	...	...	...	...	<.001 <sup>a</sup>
Hispanic	28% (46)	22% (79)	17% (111)	14% (19)	17% (7)	13% (55)	
Non-Hispanic Black	33% (54)	34% (121)	42% (276)	16% (21)	17% (7)	35% (144)	
Non-Hispanic White	28% (47)	35% (125)	34% (224)	65% (87)	59% (24)	47% (194)	
Other	11% (18)	9% (33)	8% (54)	5% (6)	7% (3)	6% (23)	
Insurance	...	...	...	...	...	...	<.001 <sup>a</sup>
None	0% (0)	1% (5)	2% (12)	3% (4)	0% (0)	1% (6)	
Public	71% (117)	70% (250)	67% (444)	44% (58)	49% (20)	51% (214)	
Private	27% (45)	28% (102)	31% (207)	53% (71)	51% (21)	47% (196)	
Other/unknown	2% (3)	0% (1)	0% (2)	0% (0)	0% (0)	0% (0)	
Received influenza vaccine	44% (72)	39% (139)	33% (221)	31% (41)	22% (9)	36% (151)	.057
Received PCV or PPSV	95% (156)	88% (316)	87% (577)	68% (91)	80% (33)	78% (326)	<.001 <sup>a</sup>
Daycare attendance, <6 years, n = 1404	23% (34)	29% (102)	33% (179)	20% (11)	24% (7)	25% (70)	.295
Any underlying comorbidity <sup>b</sup>	47% (77)	46% (165)	55% (367)	41% (54)	27% (11)	49% (204)	<.001 <sup>a</sup>
Asthma	30% (49)	30% (107)	43% (285)	28% (37)	20% (8)	29% (119)	<.001 <sup>a</sup>
Household smoke exposure	36% (60)	38% (135)	39% (259)	26% (34)	39% (16)	30% (126)	.051
Symptom duration prior to admission, days (IQR)	4.0 (2.0–5.0)	3.0 (2.0–5.0)	2.0 (1.0–4.0)	7.0 (5.0–9.0)	4.0 (2.0–8.0)	3.0 (1.0–7.0)	<.001 <sup>a</sup>
Antibiotics prior to admission	21% (34)	24% (85)	20% (131)	55% (73)	32% (13)	29% (121)	<.001 <sup>a</sup>
Clinical presentation							
Fever/feverish	97% (160)	96% (342)	87% (576)	93% (124)	95% (39)	90% (375)	<.001 <sup>a</sup>
Cough	96% (159)	99% (356)**	94% (622)	95% (127)	90% (37)	89% (371)	<.001 <sup>a</sup>
Dyspnea	64% (106)	77% (274)**	72% (480)	62% (82)	76% (31)	65% (271)	<.001 <sup>a</sup>
Retractions	42% (69)	53% (191)*	45% (299)	24% (32)	44% (18)	39% (163)	<.001 <sup>a</sup>
Wheezing	39% (64)	51% (181)*	49% (328)	25% (33)	12% (5)	28% (115)	<.001 <sup>a</sup>
Rhinorrhea	78% (129)	81% (291)	72% (478)	41% (54)	54% (22)	53% (222)	<.001 <sup>a</sup>
Abdominal pain	14% (23)	12% (44)	23% (150)	45% (60)	41% (17)	29% (121)	<.001 <sup>a</sup>
Oxygen requirement	75% (123)	72% (257)	58% (387)	64% (85)	59% (24)	50% (209)	<.001 <sup>a</sup>
WBC count > 15 × 10 <sup>3</sup>	13% (22)	17% (60)*	34% (226)	18% (24)	54% (22)	44% (183)	<.001 <sup>a</sup>
Radiographic features	...	...	...	...	...	...	<.001 <sup>a</sup>
Single lobar	20% (33)	14% (51)	23% (154)	26% (35)	34% (14)	33% (139)	
Multi lobar	21% (34)	22% (78)	23% (151)	20% (26)	37% (15)	25% (104)	
Other consolidation	1% (1)	7% (24)	7% (48)	3% (4)	5% (2)	5% (19)	
Other infiltrate	50% (83)	49% (176)	41% (271)	44% (58)	20% (8)	30% (126)	
Mixed infiltrate	8% (14)	8% (29)	6% (41)	8% (10)	5% (2)	7% (28)	
Empyema	7% (12)	4% (15)	6% (42)	21% (28)	66% (27)	19% (77)	<.001 <sup>a</sup>
Length of stay, hr, median (IQR)	68.0 (46.0–111.0)	70.5 (46.2–114.8)	55.0 (38.0–89.0)	58.0 (41.0–88.0)	160.0 (87.0–240.0)	62.5 (38.0–107.0)	<.001 <sup>a</sup>

n = 1778. "HMPV-only" indicates the detection of HMPV without the codetection of any other virus or bacteria. "RSV-only" indicates the detection of RSV without the codetection of any other virus or bacteria. "Other viral" indicates pneumonia with at least 1 other virus detected (adenovirus, coronaviruses, influenza, human rhinovirus, or parainfluenza viruses, inclusive of codetections of more than 1 of these viruses). "Atypical-only" indicates that *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, or *Legionella pneumophila* was detected without bacteria or viruses detected. "Bacterial-only" indicates the detection of typical bacteria without atypical bacteria or any virus detected. Asterisks indicate statistical significance ( $P < .05$ ) in a bivariate comparison (HMPV vs RSV; \* $P < .05$ ; \*\* $P < .01$ ; \*\*\* $P < .001$ ).

Abbreviations: HMPV, human metapneumovirus; IQR, interquartile range; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; RSV, respiratory syncytial virus; WBC, white blood cell.

<sup>a</sup> $P < .05$  was considered statistically significant and represents  $P$  values for comparisons across all groups.

<sup>b</sup>Any comorbidity, including asthma, congenital heart disease, diabetes, chronic renal disease, chronic liver disease, immunosuppression, splenectomy, prematurity (assessed if <2 years), or neurological disorder.

**Table 2. Select Characteristics of Hospitalized Adults with Human Metapneumovirus–Only Pneumonia Compared with Respiratory Syncytial Virus, Other Viral, Bacterial, and Atypical Pneumonia**

	HMPV-Only Pneumonia, n = 67, % (n)	RSV-Only Pneumonia, n = 55, % (n)	Other Viral Pneumonia, n = 391, % (n)	Atypical-Only Pneumonia, n = 74, % (n)	Bacterial-Only Pneumonia, n = 169, % (n)	No Pathogen Detected, n = 1389, % (n)	P Value
Female sex	69% (46)	62% (34)	54% (211)	43% (32)	50% (84)	50% (694)	.012 <sup>a</sup>
Median age, years (IQR)	56.0 (44.5–70.5)	64.0 (52.0–75.5)	55.0 (44.0–70.0)	51.0 (38.2–64.0)	61.0 (50.0–71.0)	58.0 (47.0–71.0)	.002 <sup>a</sup>
Age group	*						.001 <sup>a</sup>
18–49 years	34% (23)	18% (10)	36% (139)	46% (34)	22% (38)	29% (402)	
50–64 years	28% (19)	33% (18)	31% (123)	30% (22)	36% (60)	36% (494)	
65–79 years	33% (22)	29% (16)	19% (74)	18% (13)	30% (50)	22% (304)	
80 + years	4% (3)	20% (11)	14% (55)	7% (5)	12% (21)	14% (189)	
Race/ethnicity	...						.075
Hispanic	6% (4)	7% (4)	12% (48)	18% (13)	8% (14)	10% (134)	
Non-Hispanic Black	46% (31)	36% (20)	39% (151)	31% (23)	32% (54)	40% (557)	
Non-Hispanic White	43% (29)	51% (28)	45% (177)	51% (38)	57% (97)	46% (636)	
Other	4% (3)	5% (3)	4% (15)	0% (0)	2% (4)	4% (62)	
Insurance	...						.057
None	19% (13)	7% (4)	17% (67)	20% (15)	12% (20)	15% (210)	
Public	48% (32)	42% (23)	52% (202)	35% (26)	53% (89)	48% (668)	
Private	33% (22)	51% (28)	29% (114)	43% (32)	34% (57)	36% (495)	
Other/unknown	0% (0)	0% (0)	2% (8)	1% (1)	2% (3)	1% (16)	
Received influenza vaccine	36% (24)	44% (24)	40% (158)	32% (24)	35% (59)	38% (529)	.684
Received PPSV	33% (22)	42% (23)*	40% (158)	32% (24)	38% (65)	38% (524)	.367
Any underlying comorbidity <sup>b</sup>	81% (54)	73% (40)	77% (302)	58% (43)	83% (141)	79% (1099)	<.001 <sup>a</sup>
Current smoker	15% (10)	29% (16)	32% (125)	24% (18)	28% (48)	25% (346)	.158
Symptom duration prior to admission	4.0 (2.0, 7.0)	3.0 (2.0, 4.5)	4.0 (2.0, 7.0)	5.0 (3.0, 7.0)	3.0 (1.0, 7.0)	4.0 (1.0, 8.0)	.102
Antibiotics prior to admission	22% (15)	27% (15)	17% (67)	22% (16)	11% (18)	21% (293)	.027 <sup>a</sup>
Clinical presentation							
Fever/feverish	79% (53)	78% (43)	72% (283)	86% (64)	66% (112)	65% (909)	<.001 <sup>a</sup>
Cough	96% (64)	98% (54)	94% (367)	92% (68)	79% (134)	86% (1190)	<.001 <sup>a</sup>
Dyspnea	81% (54)	76% (42)	81% (318)	66% (49)	75% (126)	78% (1085)	.074
Wheezing	49% (33)	51% (28)	39% (151)	19% (14)	27% (45)	25% (342)	<.001 <sup>a</sup>
Rhinorrhea	43% (29)	62% (34)*	51% (199)	22% (16)	36% (61)	34% (473)	<.001 <sup>a</sup>
Abdominal pain	19% (13)	18% (10)	23% (89)	14% (10)	21% (36)	20% (279)	.566
O2 requirement, n = 2144	49% (33)	65% (36)	56% (220)	47% (35)	66% (112)	52% (717)	.002 <sup>a</sup>
WBC count > 15 × 10 <sup>3</sup>	13% (9)	27% (15)	19% (75)	19% (14)	39% (66)	25% (343)	<.001 <sup>a</sup>
Radiographic features	...						<.001 <sup>a</sup>
Single lobar	34% (23)	18% (10)	27% (104)	49% (36)	30% (50)	27% (375)	
Multi lobar	25% (17)	40% (22)	24% (93)	27% (20)	28% (48)	27% (372)	
Other consolidation	4% (3)	0% (0)	5% (21)	1% (1)	8% (13)	4% (56)	
Other infiltrate	31% (21)	38% (21)	38% (147)	14% (10)	28% (47)	35% (492)	
Mixed infiltrate	4% (3)	4% (2)	7% (26)	9% (7)	7% (11)	7% (94)	
Empyema	3% (2)	5% (3)	7% (27)	8% (6)	20% (34)	8% (105)	<.001 <sup>a</sup>
Length of stay, days, median (IQR)	3.0 (2.0–6.0)	3.0 (2.0–5.5)	3.0 (2.0–5.0)	3.0 (2.0–4.0)	6.0 (3.0–11.0)	3.0 (2.0–6.0)	<.001 <sup>a</sup>

n = 2145. "HMPV-only" indicates the detection of HMPV without the codetection of any other virus or bacteria. "RSV-only" indicates the detection of RSV without the codetection of any other virus or bacteria. "Other viral" indicates pneumonia with at least 1 other virus detected (adenovirus, coronaviruses, influenza, human rhinovirus, or parainfluenza viruses, inclusive of codetections of more than 1 of these viruses). "Atypical-only" indicates that *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, or *Legionella pneumophila* was detected without bacteria or viruses detected. "Bacterial-only" indicates the detection of typical bacteria without atypical bacteria or any virus detected. Asterisks indicate statistical significance ( $P < .05$ ) in a bivariate comparison (HMPV vs RSV; \* $P < .05$ ).

Abbreviations: HMPV, human metapneumovirus; IQR, interquartile range; PPSV, pneumococcal polysaccharide vaccine; RSV, respiratory syncytial virus; WBC, white blood cell.

<sup>a</sup> $P < .05$  was considered statistically significant and represents  $P$  values for comparisons across all groups.

<sup>b</sup>Any comorbidity, including chronic lung disease, chronic heart disease, diabetes, chronic renal disease, chronic liver disease, immunosuppression, splenectomy, and neurological disorder.

bacterial infections (58%). In contrast to pediatric cases, oxygen use was less common in patients with HMPV (49%) than in those with bacterial (66%) pneumonia. Single or multi-lobar

consolidation was seen on chest X-rays in 59% of HMPV cases, less commonly than in atypical pneumonia (76%), but similar to other pathogens. The presence of a parapneumonic effusion

**Table 3. Distribution of Cases of Mild, Moderate, and Severe Pneumonia by Etiology in Children and Adults**

	HMPV-Only Pneumonia, % (n)	RSV-Only Pneumonia, % (n)	Other Viral Pneumonia, % (n)	Atypical-Only Pneumonia, % (n)	Bacterial-Only Pneumonia, % (n)	No Pathogen Detected, % (n)	P Value
Children	n = 165	n = 358 <sup>a</sup>	n = 665	n = 133	n = 41	n = 416	<.001 <sup>b</sup>
Mild	76% (125)	80% (286)	80% (534)	90% (120)	56% (23)	79% (327)	
Moderate	18% (30)	14% (51)	13% (85)	9% (12)	15% (6)	13% (55)	
Severe	6% (10)	6% (21)	7% (46)	1% (1)	29% (12)	8% (34)	
Adults	n = 67	n = 55 <sup>a</sup>	n = 391	n = 74	n = 169	n = 1389	<.001 <sup>b</sup>
Mild	81% (54)	71% (39)	81% (315)	85% (63)	52% (88)	79% (1093)	
Moderate	13% (9)	11% (6)	13% (50)	12% (9)	22% (37)	12% (164)	
Severe	6% (4)	18% (10)	7% (26)	3% (2)	26% (44)	10% (132)	

Mild indicates hospitalized patients not meeting the criteria for moderate or severe disease. Moderate indicates ICU admission without meeting the severe disease criteria. Severe indicates an in-hospital death, a need for extracorporeal membrane oxygenation, acute respiratory distress syndrome, and/or requiring mechanical ventilatory support. The P values shown in the table represent the comparison among all etiologic groups listed.

Abbreviations: HMPV, human metapneumovirus; ICU, intensive care unit; RSV, respiratory syncytial virus.

<sup>a</sup>Bivariate comparisons of HMPV vs RSV were performed; P = .501 (children) and P = .108 (adults).

<sup>b</sup>P < .05 was considered statistically significant.

was less common among adults with HMPV (3%) than in those with bacterial (20%) pneumonia. Severe pneumonia occurred less commonly with HMPV (6%) than in bacterial pneumonia cases (28%).

**Clinical Severity and Length of Stay in Human Metapneumovirus Pneumonia Compared to Other Pathogens**

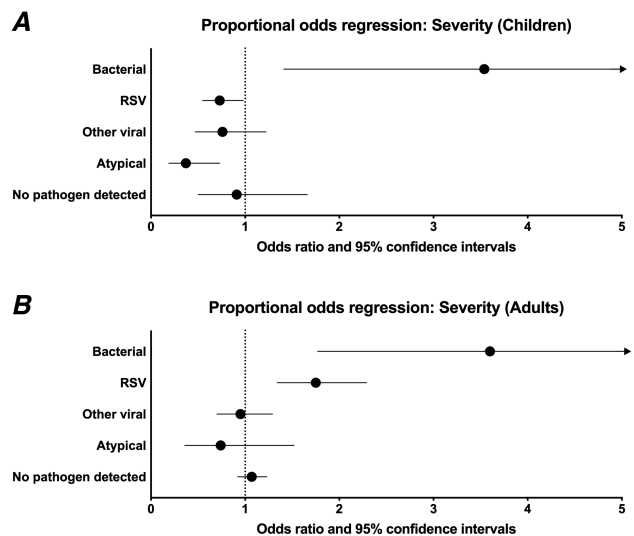
In a multivariable analysis in children, compared to HMPV pneumonia (reference), bacterial pneumonia was associated with increased severity (odds ratio [OR], 3.66; 95% confidence interval [CI], 1.43–9.40), while atypical bacterial pneumonia (OR, 0.39; 95% CI, .19–.81) and RSV (OR, 0.76; 95% CI, .59–.99) were associated with decreased disease severity (Figure 2A). The severity did not significantly differ between HMPV pneumonia and either other viruses (OR, 0.88; 95% CI, .55–1.39) or pneumonia with no pathogen detected (OR, 1.00; 95% CI, .55–1.82). Compared to HMPV, bacterial pneumonia was associated with a longer LOS (lower probability of discharge at a given time; adjusted hazard ratio [aHR], 0.40; 95% CI, .27–.61; Figure 3), whereas pneumonia caused by atypical bacteria (aHR, 1.21; 95% CI, 1.07–1.37) was associated with a decreased LOS. The lengths of stay in HMPV, RSV (aHR, 1.02; 95% CI, .83–1.24), other viral cases (aHR, 1.18; 95% CI, .97–1.43), and pneumonia with no pathogen detected (aHR, 1.03; 95% CI, .75–1.40) were similar (Figure 3).

In adults, compared to HMPV (reference), both bacterial pneumonia (OR, 3.74; 95% CI, 1.87–7.47) and RSV (OR, 1.82; 95% CI, 1.32–2.50) were associated with an increased severity of illness, while HMPV pneumonia was similar in severity to infections caused by other viruses (OR, 0.96; 95% CI, .73–1.26), atypical bacterial pathogens (OR, 0.77; 95% CI, .38–1.55), and pneumonia with no pathogen detected (OR, 1.10; 95% CI, .98–1.24; Figure 2B). Compared to HMPV, bacterial pneumonia was associated with a longer LOS (lower probability of discharge; aHR, 0.48; 95% CI, .32–.73), while the LOS was similar among

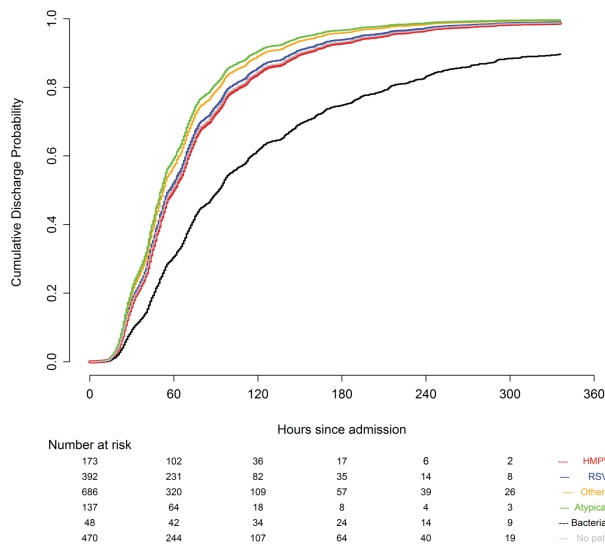
HMPV pneumonia and RSV (aHR, 1.02; 95% CI, .79–1.31), other viral (aHR, 1.11; 95% CI, .85–1.44), atypical bacterial (aHR, 1.13; 95% CI, .82–1.57), and no pathogen detected (aHR, 0.95; 95% CI, .72–1.27) pneumonia (Figure 4).

**DISCUSSION**

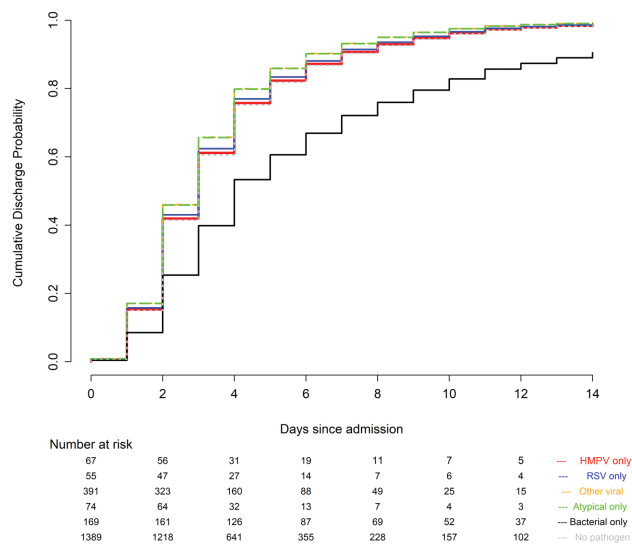
In this multi-site, population-based surveillance study, HMPV infections contributed to 12.6% and 3.8% of radiographically confirmed CAP in hospitalized children and adults, respectively.



**Figure 2.** Proportional odds regression of severity (mild, moderate, severe) by pathogen type in (A) children and (B) adults (reference values: human metapneumovirus infection, white race, male sex, single lobar chest radiographic pattern, public insurance). Circles indicate odds ratios; lines represent 95% confidence intervals. Covariates include sex, age, race, year, study site, insurance status, chest X-ray pattern, antibiotics prior to admission, duration of symptoms prior to admission, influenza and pneumococcal vaccination status, smoke exposure (household smoke exposure for children, current smoker for adults), presence of an underlying comorbidity, and presence of emphyema. Abbreviation: RSV, respiratory syncytial virus.



**Figure 3.** Proportional hazards regression of time to hospital discharge in children (hours). Covariates include sex, age, race, year, study site, insurance status, chest X-ray pattern, antibiotics prior to admission, duration of symptoms prior to admission, influenza and pneumococcal vaccination status, household smoke exposure, presence of an underlying comorbidity, and presence of empyema. Abbreviations: HMPV, human metapneumovirus; RSV, respiratory syncytial virus.



**Figure 4.** Proportional hazards regression of time to hospital discharge in adults (days). Covariates include sex, age, race, year, study site, insurance status, chest X-ray pattern, antibiotics prior to admission, duration of symptoms prior to admission, influenza and pneumococcal vaccination status, current smoking status, presence of an underlying comorbidity, and presence of empyema. Abbreviations: HMPV, human metapneumovirus; RSV, respiratory syncytial virus.

HMPV detections peaked in the late winter and early spring, and we did not observe clear evidence that HMPV detections occurred earlier the season in children than adults. No clinical features could reliably distinguish HMPV-associated pneumonia from other pneumonia etiologies. In both children and adults, HMPV infections were associated with reduced severity relative to bacterial infections. In children, HMPV infections were associated with increased severity relative to RSV and atypical bacterial infections; in adults, HMPV pneumonia was less severe than RSV and similar to other viruses.

In studies of LRTI and CAP, the prevalence of HMPV infections typically ranges from 4–10% [1, 14, 16, 22–24], although some studies have reported prevalences as high as 17–18% [25, 26]. In the CDC New Vaccine Surveillance Network study of ARI, the annual hospitalization rate associated with HMPV infections was 1:1000 children <5 years, similar to rates for influenza and parainfluenza but lower than rates of RSV [1]. In an international study of severe childhood pneumonia, HMPV was among the 10 most common pathogens at each site and was estimated to account for 7.5% of pneumonia cases [27]. In our study, the annual incidence was 1.9 pneumonia hospitalizations per 10 000 children, with the highest incidence in the youngest age group (<2 years, 8.5 per 10 000) [18]. A previous study of adults presenting to emergency departments or hospitalized with ARI found a 2.6% prevalence of HMPV, with annual hospitalization rates of 10:10 000 in those ≥50 and 2:10 000 among those 18–49 years [5]. In adults in the EPIC study, the annual incidence was 1.9 hospitalizations per 10 000 adults, with the highest incidence in the older age groups [17]. Although most previous studies focused on LRTI or ARI

and our study included only patients hospitalized with radiographically confirmed pneumonia, our range of prevalences is similar to these reports.

The median ages of children with HMPV-only and RSV-only pneumonia were 27.0 and 16.0 months, respectively, consistent with other reports that disease and hospitalizations for HMPV infections occur in slightly older children than RSV infections [15, 28–30]. In adults in our study, hospitalizations for HMPV-associated pneumonia were evenly distributed across age groups, except that adults >80 years were less often infected with HMPV.

In children and adults, HMPV pneumonia was associated with decreased severity relative to bacterial infections. In children, HMPV pneumonia was associated with increased severity relative to RSV infections. Other studies that have compared HMPV to RSV infections in children have generally reported similar severities between these 2 viruses [14, 29, 31–35], although 1 study of severe ARI reported a significantly longer duration of mechanical ventilation with HMPV compared to RSV [36], and another study of hospitalized children with an acute respiratory illness reported higher severities associated with RSV infections than HMPV [37]. Varying design and case definitions of respiratory illness (which may have been inclusive of bronchiolitis and not restricted to radiographically confirmed CAP) in other studies may limit direct comparisons to our findings. Currently, no licensed vaccines exist for HMPV, but several candidates are being evaluated [29]. Findings from our study and others support the need for additional efforts to develop a safe and effective vaccine.



Strengths of our study include active surveillance to systematically capture eligible patients using a rigorous case definition, comprehensive clinical data and sample collection, and the use of multiple modes of diagnostic testing to identify pathogens. The study also has several limitations. Not all patients had all diagnostic tests performed, including many who contributed acute but not convalescent serologies. The diagnostic tests applied have limited sensitivity, especially for bacterial detection. Moreover, bacteria may be more readily detected in cases with a complicated disease that warrants invasive procedures, thus biasing detections of bacterial pneumonia toward more severe cases. Milder, uncomplicated bacterial pneumonia cases may be underrepresented in the bacterial pneumonia group. Lower respiratory tract specimens were infrequently obtained. Antibiotic use prior to hospitalization may have reduced the yield of bacterial cultures [38]. Some pathogens were detected infrequently, making a multivariable analysis challenging; many direct comparisons of clinical features were unadjusted. Finally, our findings may be difficult to generalize to other health-care settings or geographical regions outside the United States.

In summary, no clinical characteristics were identified that could distinguish HMPV from other pathogen types at presentation, although patients with bacterial pneumonia exhibited more severe disease than those with HMPV pneumonia in both children and adults. Among children, HMPV pneumonia was associated with increased severity relative to RSV.

## Notes

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