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BRIEF REPORT

Clinical Features of Human Metapneumovirus Infection in Ambulatory Children Aged 5–13 Years

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We detected human metapneumovirus (HMPV) in 54 (5%) of 1055 children aged 5 to 13 years with acute respiratory illness (ARI) identified by outpatient and emergency department surveillance between November and May 2003–2009. Its clinical features were similar to those of HMPV-negative ARI, except a diagnosis of pneumonia was more likely (13% vs 4%, respectively; $P = .005$) and a diagnosis of pharyngitis (7% vs 24%, respectively; $P = .005$) was less likely in patients with HMPV-positive ARI than those with HMPV-negative ARI.

Keywords. acute respiratory illness; human metapneumovirus; older children.

Human metapneumovirus (HMPV) is associated with acute respiratory illness (ARI) in both children and adults [1–7]. The spectrum of disease among children can range from mild upper respiratory tract infection to lower respiratory tract involvement that presents as bronchiolitis, croup, or pneumonia [1, 2]. Many studies that have described the characteristics of HMPV infection in children were focused on infants and young children, whereas the burden and clinical features of HMPV infection among older children remain less well defined.

Using prospective population-based surveillance data from the Centers for Disease Control and Prevention (CDC)-supported New Vaccine Surveillance Network (NVSN), our group previously described the clinical features associated with HMPV infection in young children in inpatient and outpatient settings [1]. Here, we analyze data from older children (aged 5–13 years) who presented to an outpatient facility (outpatient clinic or emergency department [ED]) for medical attention to define the clinical features and etiologic role of HMPV in this age group.

METHODS

Study Design

Surveillance was conducted in the counties surrounding Cincinnati, Ohio, Nashville, Tennessee, and Rochester, New York, between November and May in 2003–2009. Children aged 5 to 13 years who had an ARI were enrolled from the outpatient department (OPD) 1 or 2 days/week; patients who presented to the ED were enrolled 1 to 4 days/week. ARI was defined as an illness that presented with fever and/or 1 or more of the following symptoms: cough, earache, nasal congestion, rhinorrhea, sore throat, vomiting after coughing, wheezing, and/or labored, rapid, or shallow breathing. Children were excluded if their symptoms were present for >14 days, if they had chemotherapy-associated neutropenia, or if they had been hospitalized within the previous 4 days. Additional details of the NVSN study design have been reported [1, 8]. After informed consent was provided by the parent/guardian, caretakers were interviewed to obtain demographic and clinical information, including underlying medical conditions, presence and duration of symptoms and signs of ARI, and complications of illness. Medical records were also reviewed for clinical and laboratory information. Information on conditions considered to confer higher risk for respiratory illnesses, including premature birth (<36 weeks' gestation), chronic pulmonary disease (including asthma), cardiac, renal, or immunodeficiency disease, cancer, or sickle cell anemia, was also obtained. Nasal and throat swabs were also obtained from each child for virologic testing [8]. After the enrollment visit, the medical records for each encounter were reviewed and recorded; the information we captured included International Classification of Diseases, Ninth Revision (ICD-9) discharge diagnosis codes assigned by the respective medical center's professional coders.

Laboratory Testing

Nasal and throat swabs were combined into a tube of transport medium and delivered at ambient temperature within 1 to 2 hours to the research virology laboratory at each site. For HMPV testing by reverse-transcription polymerase chain reaction (RT-PCR), sample aliquots were collected in lysis buffer and frozen at −70°C until shipped in batches to Vanderbilt

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University for RNA extraction and real-time RT-PCR [1]. The RT-PCR assay was designed using a dual-labeled fluorescent probe targeting the nucleoprotein (N) gene and was capable of detecting <50 RNA copies per reaction. Samples were also tested for the presence of respiratory syncytial virus (RSV) and influenza. Details of the laboratory methods were described previously [9].

Statistical Analysis

Demographic and clinical characteristics of HMPV-positive and HMPV-negative ARI in children aged 5 to 13 years were compared using Wilcoxon rank-sum and Pearson χ^2 tests as appropriate for continuous and categorical variables, respectively. We do not present population-based incidence rates because the OPD and, to a lesser extent, ED surveillance was not completely population based, as are inpatient admissions in the NVSN surveillance, although they were representative of the study population [1, 10, 11].

RESULTS

A total of 1055 children aged 5 to 13 years with ARI were enrolled and provided respiratory samples; 54 (5.1%) of them tested positive for HMPV (Table 1). In 48 (88.9%) of these 54 cases, HMPV was the only virus detected, whereas RSV was detected with HMPV in 4 (7.4%) of the 54, and influenza was codetected in 2 (3.7%) of the 54. The median age of these older ambulatory children with HMPV infection was 7 years (interquartile

Table 1. Clinical Features of HMPV Infection in Children Aged 5–13 Years[a]

Feature	HMPV-Positive Group (n = 54)	HMPV-Negative Group (n = 1001)	Total (n = 1055)	*P*[b]
Demographics and background characteristics				
Age (median [IQR]) (mo)	84.0 (72.8–114.8)	92.0 (73.0–117.0)	92.0 (73.0–118.0)	.435
Sex (n [%])				.725
Female	25 (46)	488 (49)	513 (49)	
Male	29 (54)	513 (51)	542 (51)	
Race (n [%])				.399
Black	22 (41)	542 (54)	564 (53)	
White	13 (24)	202 (20)	215 (20)	
Hispanic	13 (24)	168 (17)	181 (17)	
Other	6 (11)	88 (9)	94 (9)	
Unknown	0 (0)	1 (0)	1 (0)	
High-risk preexisting condition[c]	26 (48)	447 (45)	473 (45)	.615
Child born >1 mo early (N = 68) (n [%])	1 (25)	14 (23)	15 (23)	.964
Clinical features of illness (n [%])				
Cough	53 (98)	848 (85)	901 (85)	**.006**
Shortness of breath	27 (50)	407 (41)	434 (41)	.339
Earache	12 (22)	261 (25)	273 (26)	.589
Sore throat	34 (63)	670 (67)	704 (67)	.759
Fever	35 (65)	713 (71)	748 (71)	.511
Vomiting after cough	20 (37)	260 (26)	280 (27)	.196
Nasal congestion/rhinorrhea	44 (81)	778 (78)	822 (78)	.517
Wheezing	27 (50)	364 (36)	391 (37)	.113
Poor appetite	29 (54)	590 (59)	619 (59)	.609
Discharge diagnosis (n [%])				
Asthma	13 (24)	198 (20)	211 (20)	.442
Croup	0 (0)	7 (1)	7 (1)	.538
Fever	3 (6)	78 (8)	81 (8)	.548
Influenza	1 (2)	23 (2)	24 (2)	.831
Otitis media	10 (19)	112 (11)	122 (12)	.101
Pharyngitis	4 (7)	240 (24)	244 (23)	**.005**
Pneumonia	7 (13)	45 (4)	52 (5)	**.005**
Sinusitis	2 (4)	23 (2)	25 (2)	.508
Upper respiratory infection	18 (33)	279 (28)	297 (28)	.385
Viral illness	1 (2)	44 (4)	45 (4)	.368
Other acute respiratory illness	7 (13)	38 (4)	45 (4)	**.001**
Bronchiolitis	2 (4)	8 (1)	10 (1)	**.032**

Bold type indicates a statistically significant result, with statistical significance considered for $P < .05$. Abbreviations: HMPV, human metapneumovirus; IQR, interquartile range.

[a]N = 1055, except as specified.

[b]Bold type indicates a significant result.

[c]High-risk preexisting conditions for more severe respiratory illness include premature birth (<36 weeks' gestation), chronic pulmonary disease including asthma, cardiac, renal, or immunodeficiency disease, cancer, and sickle cell anemia.

range, 6–9 years), and similar proportions of boys and girls were affected. In the 54 HMPV-positive children, cough, rhinorrhea, fever, and sore throat were the most common features (present in 98%, 81%, 65%, and 63% of these children, respectively). Wheezing, shortness of breath, and decreased appetite were also present in approximately half of the children with HMPV infection. Earache and posttussive emesis were uncommon.

Of the 54 children with HMPV infection, 22 (41%) presented to an ED, and 32 (59%) presented to an OPD. Ages and comorbidities present were similar among the children who presented to an ED and those who presented to an OPD, and the proportions of children with HMPV among those enrolled in an ED (22 [4.7%] of 464) and those enrolled in an OPD (32 [5.4%] of 591) were similar ($P = .622$). However, children with HMPV who presented to an ED were significantly more likely to have shortness of breath (17 [77%] of 22) or wheezing (16 [73%] of 22) as a presenting complaint than those who presented to an OPD (shortness of breath, 10 [31%] of 32, $P < .001$; wheezing, 11 [34%] of 32, $P = .006$]. Among all 464 patients who presented to an ED, those with HMPV infection were more likely to present with wheezing (16 [73%] of 22) or dyspnea (17 [77%] of 22) than those who tested HMPV negative (wheezing, 192 [43%] of 442, $P = .01$; dyspnea, 214 [48%] of 442, $P < .01$). In addition, children who presented to an ED were significantly more likely to have a discharge diagnosis of asthma (10 [45%] of 22) and less likely to be diagnosed with otitis media (1 [5%] of 22) than those who presented to an OPD (asthma, 3 [9%] of 32, $P = .002$; otitis media, 9 [28%] of 32, $P = .028$).

A previous diagnosis of asthma was present in 437 (41.4%) of 1055 of the study children. Cough was a presenting symptom in 389 (89%) of 437 of those with an underlying diagnosis of asthma and in 512 (83%) of 618 of those without an underlying diagnosis of asthma ($P = .005$). Children with a preexisting diagnosis of asthma were significantly more likely to have a discharge diagnosis of asthma (200 [45.8%] of 437) but not more likely to have a discharge diagnosis of pneumonia (26 [5.9%] of 437) than those without a preexisting diagnosis of asthma (asthma, 11 [1.8%] of 618, $P < .001$; pneumonia, 26 [4.2%] of 618, $P = .198$). The difference in detection of HMPV during ARI in children with a preexisting diagnosis of asthma (25 [5.7%] of 437) compared to those without this preexisting diagnosis (29 [4.7%] of 618) was not statistically significant ($P = .455$).

Cough was present more frequently in children with HMPV infection (53 [98%] of 54) than in those with HMPV-negative ARI (848 [85%] of 1001; $P = .006$). Otherwise, there were no significant differences in the clinical features of HMPV infections compared to those of infections in which HMPV was not detected (Table 1). In addition, we found no difference between the proportions of high-risk preexisting conditions in the HMPV-positive group and those in the HMPV-negative group. However, children with an infection in which HMPV was detected were significantly more likely to be assigned a discharge diagnosis code of pneumonia, other ARI, or bronchiolitis than children with HMPV-negative infection and were less likely to be assigned a discharge diagnosis code of pharyngitis. Of all 1055 study children, 29 (2.7%) were hospitalized and 4 (0.4%) required supplemental oxygen. None of the hospitalized older children had HMPV, and none of the 4 children who required oxygen had HMPV infection.

DISCUSSION

Here, we report that HMPV was detected in 5% of children aged 5 to 13 who presented to an outpatient or ED setting with ARI; those with HMPV-positive ARI had clinical features similar to those with ARI for which HMPV was not detected. The only clinical feature of HMPV infection observed in our cohort that differed significantly from those with HMPV-negative ARI was cough, which was present almost universally (53 [98%] of 54) in children with HMPV infection. This result suggests that HMPV ARI is associated with a higher proportion of lower respiratory tract disease than HMPV-negative ARI, particularly given that HMPV infection was also associated with an incidence of coded pneumonia or bronchiolitis diagnosis that was higher than that in the HMPV-negative group. A preexisting asthma diagnosis was associated with a discharge diagnosis of asthma, although it was not significantly associated with detection of HMPV or a discharge diagnosis of pneumonia.

The clinical features of infection we observed in older children with HMPV infection were similar to characteristics previously reported for HMPV-infected children <5 years old enrolled in the NVSN [1]. In the study of younger children with ARI, HMPV was detected in 7% of children evaluated in an outpatient clinic or ED and in 6% of hospitalized children. Hospitalized patients with HMPV-positive ARI were significantly older than HMPV-negative patients and were more likely to have a high-risk preexisting condition. However, no significant association with preexisting conditions was observed in the outpatient/ED setting in the younger children or in our current cohort of older children.

Although HMPV infection was common in this older cohort with ARI, no HMPV-positive children aged 5 to 13 years were hospitalized. Rates of HMPV-associated hospitalization are highest among children <6 months old, but the rates of HMPV-associated outpatient visits among children aged 6 to 59 months remain similar to the rates among young infants [1]. This pattern is in contrast to that observed for RSV and coronavirus infection, for which rates of symptomatic illness and hospitalization decrease markedly after 1 year of age [10, 11]. Thus, our findings support the assertion that HMPV, similar to influenza [12], causes clinically significant disease not only during early childhood but also throughout later childhood.

This observation is further supported by findings from another multicenter prospective population-based study of hospitalized children with pneumonia in which the incidence of HMPV-associated pneumonia was highest among children <5 years old but also remained prevalent in 5- to 9- and 10- to 17-year-old children [7].

In a retrospective cohort study at a US children's hospital, 90 (11.0%) of 815 hospitalized children with HMPV infection were aged 5 to 17 years [13]. The authors estimated that HMPV results in approximately 27 000 hospitalizations annually in children aged <18 years (mean estimated cost, $277 million (95% confidence interval, $246–$308 million). An additional 1060 HMPV infections occurred that were associated with outpatient visits, ED visits, or brief (<24-hour) hospitalizations. Although those 1060 episodes associated with outpatient visits, ED visits, and brief hospitalizations were not stratified according to age, the prevalence of HMPV detection among outpatients in our study suggests that children aged >5 years might contribute substantially to this burden.

Our study has several limitations. First, the study population might not be representative of the entire US population or that of other locations, despite the large number of patients enrolled at our 3 study sites. Second, children were enrolled only between November and May. Thus, our estimate might not represent the overall outpatient/ED burden of HMPV infection in older children, given that HMPV infection has been associated with biannual periodicity in some studies, and its seasonality might extend beyond May [13]. We enrolled children in outpatient and ED settings but not inpatients, although patients seen in outpatient and ED settings who were admitted were included. Thus, detailed features of more complicated or severe HMPV infections in older children who were directly admitted to the hospital were not captured in our study. Moreover, the numbers enrolled did not allow us to calculate rates of HMPV-associated hospitalization among older children. Our analysis did not examine the clinical features of infections with viruses other than HMPV, so direct comparisons of the features of HMPV infection with those of other viruses in older children cannot be made.

In conclusion, HMPV is detected in approximately 1 in 20 older children with ARI who present to an outpatient or ED setting for medical attention. Although outpatient HMPV ARI is less severe and costly than ARI that requires hospitalization, the number of outpatient ARIs associated with HMPV in older children likely represents a substantial health care burden among all children.

Notes

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Potential conflicts of interest. J. V. W. serves on the scientific advisory board of Quidel and an independent data-monitoring committee for GlaxoSmithKline. The other authors report no conflicts. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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