Population-Based Incidence of Human Metapneumovirus Infection among Hospitalized Children

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Background. Human metapneumovirus (HMPV) is a leading cause of acute respiratory illness (ARI) in children. Population-based incidence rates and comprehensive clinical characterizations of disease have not been established.

Methods. We conducted population-based prospective surveillance for 2 years in 2 US counties of HMPV infection among children <5 years old who were hospitalized with ARI or fever. Nasal and throat specimens obtained with swabs were tested for HMPV by real-time reverse-transcription polymerase chain reaction and genotyped.

Results. Forty-two (3.8%) of 1104 children tested positive for HMPV. The overall annual rate of HMPV-associated hospitalizations per 1000 children <5 years old was 1.2 (95% confidence interval [CI], 0.9–1.6). This rate was highest among infants 0–5 months old (4.9 per 1000 [95% CI, 2.9–7.2]), followed by children 6–11 months old (2.9 per 1000 [95% CI, 1.4–4.7]). The annual rate of hospitalization for HMPV infection was less than that for respiratory syncytial virus infection but similar to that for influenza and parainfluenza virus 3 infection in all age groups. The mean age of children hospitalized with HMPV infection was 6 months. Bronchiolitis, pneumonia, and asthma were the most common diagnoses among children with HMPV infection. All 4 HMPV subgroups were detected during both years at both sites. HPMV infection was most prominent from March through May.

Conclusion. HMPV was detected in 3.8% of children hospitalized with ARI or fever, with a population incidence similar to that of influenza virus and parainfluenza virus 3.
by the age of 5 years [3, 16–18]. Previous estimates of the percentage of acute pediatric lower respiratory tract infections associated with HMPV range from 5% to 25% [2, 4, 5, 7, 19–21], with differences likely resulting from various geographic areas being studied, seasonal variability in HMPV circulation, methodological differences, and age groups evaluated. Reinfection occurs throughout life, but subsequent infections are more likely to present with upper respiratory symptoms than with lower respiratory symptoms and to be milder in character than primary infection [1, 2].

Despite studies demonstrating the prevalence of HMPV infection, its actual population-wide disease burden is poorly understood. This study had 3 objectives. First, we sought to establish population-based rates of HMPV-associated infection in hospitalized children <5 years old with acute respiratory symptoms or fever. Second, we sought to compare the burden of HMPV infection with that of other respiratory virus infections. Finally, although earlier studies outlined the clinical characteristics of HMPV infection on convenience samples, we wished to comprehensively characterize the clinical presentations from a population-wide perspective.

METHODS

Study design. The New Vaccine Surveillance Network was established by the Centers for Disease Control and Prevention to determine the burden of acute respiratory illness (ARI) from vaccine-preventable or potentially preventable agents and to monitor the impact of vaccine use on disease rates [22]. Prospective population-based surveillance was conducted among children <5 years of age who were hospitalized with acute respiratory symptoms or fever anytime from 1 October 2001 through 30 September 2003 in area hospitals that provided care for >95% of hospitalized children in Davidson County, Tennessee (Nashville), and Monroe County, New York (Rochester). The institutional review boards at both study sites, the participating hospitals, and the Centers for Disease Control and Prevention approved the study.

The current study used previously published methods to establish the burden of HMPV infection in hospitalized children [23–25]. Eligible hospitalized children were <5 years of age and had received an admission diagnosis of fever alone or of acute respiratory infection, which was defined as an illness presenting with fever and/or 1 or more of the following symptoms: cough, earache, nasal congestion, rhinorrhea, sore throat, vomiting after coughing, wheezing, and labored, rapid, or shallow breathing. Children were excluded if they had respiratory symptoms that had lasted >14 days at the time of admission, had neutropenia from chemotherapy, were hospitalized elsewhere within the preceding 4 days, or were newborns who had been hospitalized since birth. Study nurses enrolled children admitted to surveillance hospitals from Sunday through Thurs-

day, after obtaining written informed consent. Children were eligible for enrollment if they were admitted within 48 h of an enrollment day. Nasal and throat specimens were obtained with swabs from all children on the day of enrollment (thus within 48 h of admission), combined into a single tube of viral transport medium, and promptly delivered to the research laboratories at the study sites. Demographic and clinical information was collected using a standardized questionnaire, as described elsewhere [22, 26]. We performed statistical comparisons between children infected with HMPV alone and children infected with other specific viruses alone; children with >1 virus detected in their specimens were excluded from analysis. Children were considered to be virus-negative if their specimens tested negative for HMPV, influenza virus, respiratory syncytial virus (RSV), parainfluenza virus (PIV), human rhinovirus (HRV), and human coronavirus by testing methods that are described below. High-risk conditions were assessed, which included history of asthma, heart disease, sickle cell anemia, cystic fibrosis, diabetes mellitus, and neuromuscular conditions such as seizures, cerebral palsy, or muscular dystrophy. History of asthma was determined by asking the parents if their child had ever received a diagnosis of asthma from any health care provider or by documentation of a previous diagnosis of asthma in the medical record [24].

Molecular testing. Specimens were divided into aliquots and stored at −80°C until processing. RNA was extracted from pooled nasal and throat swab medium. Specimens were tested for HMPV by real-time reverse-transcription polymerase chain reaction (RT-PCR), as described elsewhere [1, 27]. Specimens were also tested for influenza virus, RSV, PIV, HRV, and human coronavirus by real-time RT-PCR [23–25, 28, 29]. Specimens that tested positive for HMPV were subjected to conventional nested RT-PCR to amplify and sequence complementary DNA of the F and G genes, as described elsewhere [1]. HMPV subgroup assignment was made on the basis of either the F or the G gene; either gene reliably identifies the viral subgroup [30]. Sequences were edited and aligned with published HMPV sequences obtained from GenBank by means of the ClustalW algorithm in MacVector software (version 10.0; Accelrys). Phylogenetic analyses were performed using Mega software (version 4) [31]. The data sets were resampled with 500 bootstraps, distances were computed using the maximum composite likelihood method, and phylogeny was inferred using the neighbor-joining method [31]. Analyses that made use of the maximum parsimony and minimum evolution methods yielded similar results (data not shown), and so only the results of the neighbor-joining analysis are shown.

Data analysis. The number of hospitalized children with laboratory-confirmed HMPV infection per 1000 children was calculated as the weighted number of HMPV-positive hospitalized children with ARI or fever divided by the number of children in the county population as determined by the 2000
US Census, multiplied by 1000 [22–26, 29]. Rates were calculated by weighting the observed number of enrolled hospitalized children to account for sampling 5 days per week and eligible patients who were not enrolled. Rates were determined overall and by demographic subsets with 95% confidence intervals (CIs) calculated using 1000 bootstrap samples.

Kruskal-Wallis or Pearson tests were used as appropriate for contingency table analyses of signs and symptoms associated with HMPV infection alone compared with infection with RSV, influenza virus, PIV, or HRV alone, or compared with virus-negative children. Influenza virus included influenza A and B viruses; PIV included PIV types 1, 2, and 3. For comparative analyses, children with coinfections were excluded. Prospectively collected demographic and clinical data were compared among children with different viral infections and virus-negative children. Age was categorized as 1 of 3 groups (<6, 6–23, and >23 months), on the basis of prior studies of respiratory viruses among this population [22, 23, 25, 26, 29]. All analyses were performed using R software (version 2.6.2; see http://www.R-project.org).

**RESULTS**

**Study population.** Of 1298 children admitted to the surveillance hospitals with respiratory symptoms or fever during enrollment days over the 2-year period, 1123 (86.5%) were enrolled. Of 175 children who were not enrolled, 87 (49.7%) had parents and/or guardians who refused participation, 62 (35.4%) did not want to participate, and the remaining 26 (14.9%) were defined as unknown or refusal.

**Table 1. Characteristics of Hospitalized Children with Human Metapneumovirus (HMPV) Infection Compared with Those of Other Study Children**

| Characteristic       | HMPV alone (N = 29) | RSV alone (N = 142) | Influenza virus alone (N = 45) | PIV alone (N = 56) | HRV alone (N = 141) | None (N = 588) | P   |
|----------------------|---------------------|---------------------|-------------------------------|-------------------|---------------------|----------------|-----|
| Age in months, median (range) | 6 (2–13) | 4 (1–14) | 4 (1–14) | 13 (6–23) | 14 (3–30) | 5 (1–18) | <.001* |
| Age group <6 months | 14 (48) | 80 (56) | 25 (56) | 14 (25) | 45 (32) | 295 (50) | <.001b |
| 6–23 months         | 9 (31) | 54 (38) | 12 (27) | 28 (50) | 48 (34) | 185 (31) |       |
| 24–59 months        | 6 (21) | 8 (6) | 8 (18) | 14 (25) | 48 (34) | 108 (18) |       |
| Female sex          | 13 (45) | 61 (43) | 26 (58) | 23 (41) | 64 (45) | 259 (44) | .592b |
| Race or ethnicity   | 7 (24) | 79 (56) | 18 (40) | 25 (45) | 55 (39) | 277 (47) | .132b |
| White                | 13 (45) | 39 (27) | 13 (29) | 21 (38) | 50 (35) | 200 (34) |       |
| Black                | 9 (31) | 20 (14) | 11 (24) | 8 (14) | 25 (18) | 78 (13) |       |
| Hispanic             | 0 (0) | 4 (3) | 3 (7) | 2 (4) | 10 (7) | 31 (5) |       |
| Insurance            | 22 (76) | 70 (49) | 26 (58) | 27 (48) | 59 (42) | 307 (52) | .184b |
| Public               | 5 (17) | 59 (42) | 16 (36) | 23 (41) | 65 (46) | 224 (38) |       |
| Private              | 2 (7) | 13 (9) | 3 (7) | 6 (11) | 16 (11) | 57 (10) |       |
| None                 | 6 (21) | 56 (39) | 10 (22) | 24 (43) | 53 (38) | 170 (29) | .011b |
| Daycare              | 14 (48) | 54 (38) | 21 (47) | 21 (38) | 56 (40) | 225 (38) | .042b |
| Smoking in home      | 5 (17) | 21 (15) | 2 (4) | 4 (7) | 9 (6) | 88 (15) | .134b |
| Premature birth      | 11 (38) | 30 (21) | 9 (20) | 16 (29) | 64 (45) | 161 (27) | <.001b |
| High risk            | 6 (21) | 26 (18) | 4 (9) | 16 (29) | 49 (35) | 108 (18) | <.001b |
| History of asthma    | <6 months | 14 (48) | 80 (56) | 25 (56) | 14 (25) | 45 (32) | 295 (50) | <.001b |
| Study site           | 15 (52) | 53 (37) | 28 (62) | 35 (62) | 61 (43) | 406 (69) |       |
| Nashville            | 14 (48) | 89 (63) | 17 (38) | 21 (38) | 80 (57) | 182 (31) |       |
| Rochester            | Year 1 | 17 (59) | 75 (53) | 31 (69) | 25 (45) | 67 (48) | 360 (61) | .005b |
| Study year           | Year 2 | 12 (41) | 67 (47) | 14 (31) | 31 (55) | 74 (52) | 228 (39) | .8b  |

**NOTE.** Data are no. (%) of children, unless otherwise indicated. The group of children who tested negative for all viruses includes all children for whom no virus was identified by means of testing as described in Methods. The influenza virus group includes influenza A and B viruses combined. Discharge diagnoses were mutually exclusive by the order of listed discharge diagnoses—that is, if a patient had both asthma and bronchiolitis, the patient was counted as having asthma for this grouped statistical comparison. Some data were unknown for some subjects. HRV, human rhinovirus; PIV, parainfluenza virus types 1, 2, and 3 combined; RSV, respiratory syncytial virus.

* Kruskal-Wallis test.

b Pearson test.
Table 2. Incidence of Hospitalization Attributable to Infection with Human Metapneumovirus (HMPV) and Other Common Respiratory Viruses among Children <5 Years Old

| Age group   | HMPV (Infections per 1000 children, 95% CI) | RSV (Infections per 1000 children, 95% CI) | Influenza virus (Infections per 1000 children, 95% CI) | PIV-3 (Infections per 1000 children, 95% CI) |
|-------------|-------------------------------------------|-------------------------------------------|------------------------------------------------------|--------------------------------------------|
| 0–5 months  | 4.9 (2.9–7.2)                              | 16.9 (15.3–18.5)                          | 4.5 (3.4–5.5)                                        | 1.6 (1.0–2.2)                              |
| 6–11 months | 2.9 (1.4–4.7)                              | 5.1 (4.6–5.6)                             | 0.9 (0.7–1.2)                                        | 1.0 (0.6–1.6)                              |
| 12–23 months| 0.7 (0.1–1.4)                              | 2.7 (2.3–2.7)                             | ...                                                  | 0.7 (0.5–1.0)                              |
| 24–59 months| 0.4 (0.1–0.7)                              | 0.4 (0.3–0.4)                             | 0.3 (0.2–0.5)                                        | 0.2 (0.1–0.2)                              |
| Overall     | 1.2 (0.9–1.6)                              | 3.0 (2.8–3.4)                             | 0.9 (0.8–1.1)                                        | 0.5 (0.4–0.6)                              |

**NOTE.** Data on respiratory syncytial virus (RSV), influenza virus, and parainfluenza virus 3 (PIV-3) are from hospitalized children <5 years old in the New Vaccine Surveillance Network, obtained using the same sampling techniques [23, 25, 29]. Influenza virus includes influenza A and B viruses. CI, confidence interval.

* Combined HMPV infection rate for children aged 6–23 months is 1.4 (95% CI, 0.8–2.2).

* Influenza rate in this age group is for children aged 6–23 months.
Table 3. Clinical Features of Human Metapneumovirus-Positive and Human Metapneumovirus-Negative Hospitalized Children

| Characteristic                | HMPV alone (N = 29) | RSV alone (N = 142) | Influenza virus alone (N = 45) | PIV alone (N = 56) | HRV alone (N = 141) | None (N = 888) | P  a |
|------------------------------|---------------------|---------------------|--------------------------------|-------------------|--------------------|----------------|------|
| Fever                        | 22 (76)             | 94 (66)             | 42 (93)                        | 46 (82)           | 99 (70)            | 451 (77)       | .011 |
| Rhinorrhea and/or congestion | 21 (72)             | 133 (94)            | 32 (71)                        | 46 (82)           | 113 (80)           | 419 (71)       | <.001|
| Cough                        | 25 (86)             | 141 (99)            | 37 (82)                        | 54 (96)           | 121 (86)           | 416 (71)       | <.001|
| Poor appetite                 | 21 (72)             | 109 (77)            | 32 (71)                        | 43 (77)           | 89 (63)            | 320 (54)       | <.001|
| Difficulty breathing          | 27 (93)             | 137 (96)            | 25 (56)                        | 47 (84)           | 107 (76)           | 408 (69)       | <.001|
| Wheezing                     | 11 (38)             | 52 (37)             | 5 (11)                         | 24 (43)           | 43 (30)            | 120 (20)       | <.001|
| Sore throat                  | 7 (24)              | 10 (7)              | 4 (9)                          | 12 (21)           | 13 (9)             | 44 (7)         | <.001|
| Supplemental oxygen          | 11 (38)             | 84 (59)             | 10 (22)                        | 16 (29)           | 45 (32)            | 162 (28)       | <.001|
| ICU stay                     | 1 (3)               | 3 (2)               | 1 (2)                          | 2 (4)             | 7 (5)              | 22 (4)         | .621 |
| Death                        | 0                   | 1 (1)               | 0                              | 0                 | 1 (1)              | 1 (< 1)        | .399 |
| Discharge diagnosis          |                     |                     |                                |                   |                    |                |      |
| Bronchiolitis                | 11 (38)             | 76 (54)             | 6 (13)                         | 2 (4)             | 8 (6)              | 100 (17)       | <.001|
| Asthma                       | 7 (24)              | 37 (26)             | 4 (9)                          | 16 (29)           | 65 (46)            | 138 (23)       |      |
| Pneumonia                    | 7 (24)              | 23 (16)             | 6 (13)                         | 7 (12)            | 25 (18)            | 81 (14)        |      |
| URTI                         | 1 (3)               | 2 (1)               | 5 (11)                         | 2 (4)             | 11 (8)             | 31 (6)         |      |
| Other                        | 3 (10)              | 4 (3)               | 24 (53)                        | 29 (52)           | 31 (22)            | 238 (40)       |      |

NOTE. Data are no. (%) of children. The group of children who tested negative for all viruses includes all children for whom no virus was identified by means of testing as described in Methods. The influenza virus group includes influenza A and B viruses combined. Discharge diagnoses were mutually exclusive by the order of listed discharge diagnoses—that is, if a patient had both asthma and bronchiolitis, the patient was counted as having asthma for this grouped statistical comparison. Some data were unknown for some subjects. HMPV, human metapneumovirus; HRV, human rhinovirus; ICU, intensive care unit; PIV, parainfluenza virus types 1, 2, and 3 combined; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection.

a Pearson test.
first year and A2 and B1 detected with equal frequency in the second year (Figure 2). There were no differences between the prevalence of the subgroups by study site. No differences in disease severity were noted between the subgroups (data not shown). Phylogenetic analysis showed genetic diversity even within each of these subgroups, with analysis of the F gene sequences showing 2 sublineages of the A2 subgroup (Figure 3A) and analysis of the G gene sequences showing 2 sublineages of the B1 subgroup (Figure 3B). Both of these sublineages circulated during the same season and at the same study site and thus were not unique to either site or year.

**DISCUSSION**

We used prospective, population-based, laboratory-confirmed active surveillance to define the burden of HMPV infection among hospitalized young children. The contribution of HMPV infection to pediatric hospitalization for ARI or fever was substantial, with 1.2 hospitalizations per 1000 children <5 years old per year (95% CI, 0.9–1.6), compared with 3.0 per 1000 (95% CI, 2.8–3.4) for RSV, 0.9 per 1000 (95% CI, 0.8–1.1) for influenza virus, and 0.5 per 1000 (95% CI, 0.4–0.6) for PIV-3 [23, 25, 29]. The rate of HMPV-associated hospitalization was highest among infants 0–5 months old, at 4.9 per 1000 (95% CI, 2.9–7.2), compared with 16.9 per 1000 (95% CI, 15.3–18.5) for RSV, 4.5 per 1000 (95% CI, 3.4–5.5) for influenza virus, and 1.6 per 1000 (95% CI, 1.0–2.2) for PIV-3 [23, 25, 29]. These data suggest that HMPV causes hospitalizations for respiratory symptoms and fever in children <5 years old at rates similar to those of influenza.
virus and PIV. If we extrapolate from US Census data, then our data would project ~27,000 HMPV-related hospitalizations of children <5 years of age annually, which underscores the impact of HMPV infection on children. HMPV is rarely detected in asymptomatic young children [2, 3, 32, 33].

Although there have been reports of HMPV disease in children with underlying medical conditions, such as premature birth or asthma, few of these studies have been population-based and have enrolled as many children as were enrolled in the present study [8, 11–15, 19, 34, 35]. One-third of the hospitalized children with HMPV infection in our study had high-risk conditions, which suggests that these children are at higher risk for hospitalization with HMPV infection. However, two-thirds of HMPV-infected hospitalized children were otherwise healthy children. We did not observe an association between HMPV hospitalization and a history of asthma, in contrast to the association between asthma and HRV infection that was previously found in this cohort [24, 36]. Consistent with previous reports, HMPV infection was associated most frequently with a diagnosis of bronchiolitis [2, 5, 7, 19, 21]. The presenting symptoms of HMPV infection in this cohort generally were not distinct from those of children infected with other viruses, consistent with other reports [1, 2, 5, 7, 19, 21, 37, 38]. However, very few HMPV-infected children (5%) had fever alone without respiratory symptoms.

HMPV infection was most prominent at both study sites during the late winter and spring months, with peak illness rates in March, April, and May. Overall, HMPV infection accounted for up to 15% of all hospitalizations for children ≤5 years old with ARI or fever with a late spring distribution and was more common than influenza or RSV infection during this time period [23, 25]. However, the lack of distinctive clinical symptoms and the overlap with other community respiratory virus infections highlights the potential utility of rapid, sensitive diagnostic tests such as RT-PCR to detect HMPV and other respiratory viruses.

We identified all 4 subgroups of HMPV during each year and at each study site, although the distribution of subgroups varied by year. The extent of antigenic variability between HMPV subgroups is not clear in animals or in humans [30, 39–41], but the presence of multiple HMPV strains in a single season could affect the design of vaccines or prophylactic antibodies if antigenic variability leads to partial immune escape. We did not find that specific subgroups were associated with more severe disease (data not shown); some studies have suggested this phenomenon [42], whereas others have not [43]. Correlation between infecting subtype and disease severity has been shown for RSV infection [44, 45]. A postulated mechanism for alternating circulation of different HMPV subgroups is population immune pressure [46, 47]. Long-term, prospective, population-based surveillance is needed to establish whether different subgroups of HMPV vary in virulence and whether circulation patterns are the result of immune pressure.

**Study limitations.** Despite the strength of our prospective population-based surveillance system, our study had limitations. First, surveillance was performed for only 2 years at only 2 geographically distant sites (representing 2 US regions, Northeast and South). Greater regional and temporal differences in viral circulation may have been evident if the study included more years or sites, because other studies have reported substantial year-to-year variability in HMPV infection prevalence [1]. Second, institutional differences in medical practice might have contributed to variation in HMPV-related hospitalization rates, and although enrolled and nonenrolled children did not differ in demographic characteristics, unknown biases may have affected our HMPV infection burden estimates. Coinfections were present in a minority of children, but the clinical importance of these coinfections is not clear. HRV is identified frequently in asymptomatic individuals and thus is especially difficult to interpret as a codetected virus [48–50]. A large number of children in the study did not have a virus identified by means of the testing used; this could be attributable to false negative test results or to the presence of other pathogens for which we did not test. Nearly all of the HMPV-infected children had ARI symptoms and not fever alone, but we enrolled children with fever alone in addition to children with ARI. Thus, because the population-based incidence was calculated with all hospitalized children, including those with fever alone, we may have underestimated the true incidence of infection with HMPV (and other viruses) among children with ARI. Finally, this study only assessed hospitalized children, and the impact of HMPV infection on emergency department and outpatient visits is unknown.

**Conclusion.** HMPV infection is a leading cause of hospitalization for ARI among children <5 years of age, with a population-based incidence similar to that of influenza and PIV-3 infection. The majority of HMPV-associated hospitalizations occurred among otherwise healthy children. These data suggest a need for preventive and therapeutic strategies for HMPV infection and highlight the need to consider HMPV infection as a cause of ARI among hospitalized children, especially in the spring.

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HMPV Infection in Hospitalized Children • JID 2010:201 (15 June) • 1897
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