Published in final edited form as:
J Infect Dis. 2005 September 15; 192(6): 1061–1065.

A Prospective Study Comparing Human Metapneumovirus with Other Respiratory Viruses in Adults with Hematologic Malignancies and Respiratory Tract Infections

John V. Williams[1], **Rodrigo Martino**[3], **Núria Rabella**[4], **Magdalena Otegui**[4], **Rocio Parody**[3], **Joshua M. Heck**[1], and **James E. Crowe Jr.**[1,2]

1 *Departments of Pediatrics and*

2*Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee;*

3*Division of Clinical Hematology and*

4*Department of Microbiology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

Abstract

Human metapneumovirus (hMPV) is a recently described paramyxovirus associated with upper and lower respiratory-tract infection (URI and LRI, respectively). We conducted a prospective study of URI and LRI in adults with hematologic malignancies during a 4-year period. We retrospectively tested samples by reverse-transcription polymerase chain reaction for hMPV and analyzed clinical data. Twenty-two (9%) of 251 episodes of respiratory infection tested positive for hMPV. Sixteen (73%) of the illnesses occurred in hematopoietic stem-cell transplant recipients. Nine patients with hMPV developed LRI; 3 of these patients died. hMPV is a common cause of respiratory infections in adults with hematologic malignancies, with associated morbidity and mortality.

Respiratory viruses—including respiratory syncytial virus (RSV), influenza virus, and parainfluenza virus (PIV)—have been associated with severe pneumonia in patients receiving chemotherapy, especially in hematopoietic stem-cell transplant (HSCT) recipients [1–8]. Human metapneumovirus (hMPV) is a recently described paramyxovirus that has been associated with acute upper and lower respiratory-tract infection (URI and LRI, respectively) in children and adults [9–13]. There have been 2 reports of fatal hMPV infection in patients with leukemia [14,15]. We retrospectively tested samples from a previous prospective study of respiratory virus infections in adults with hematologic malignancies [5], to determine the epidemiological and clinical features of hMPV infection in these patients.

Patients and methods

The present prospective study was conducted at the Division of Clinical Hematology, Hospital de la Santa Creu i Sant Pau (Barcelona, Spain), from 1 October 1999 through 31 July 2004. All inpatient or outpatient adults with a hematologic malignancy (including HSCT recipients) who had signs and symptoms of URI or LRI underwent a detailed clinical evaluation. Patients with symptoms of URI underwent nasopharyngeal aspiration (NPA), whereas patients with LRI underwent bronchoalveolar lavage (BAL) when it was clinically possible. Patients with

Reprints or correspondence: Dr. John V. Williams, Dept. of Pediatrics, Div. of Pediatric Infectious Diseases, Vanderbilt University Medical Center, D-7235 Medical Center North, 1161 21st Ave. South, Nashville, TN 37232-2581 (john.williams@vanderbilt.edu)..

Financial support: Fondo de Investigaciones Sanitarias (grant FIS 00/0296 to R.M.); National Institutes of Health (grant R03-AI54760 to J.V.W.).

Potential conflicts of interest: none reported.

pneumonia but no signs of URI did not undergo NPA. The study was approved by the institutional review board of both author-affiliated institutions.

URI was defined as new onset of nasal, pharyngeal, or laryngeal irritation. LRI was defined as cough, rales, and/or wheezing in conjunction with a new pulmonary infiltrate identified on a chest radiograph. Progression of URI to LRI was defined as the development of pneumonia in patients with prior or concurrent URI. Patients with a diagnosis of pneumonia in the absence of URI were considered to have an isolated LRI. Respiratory virus infections were considered to be nosocomial if the onset of illness occurred after the patient had been hospitalized for ⩾3 days. We defined death from pneumonia as that which occurred when a patient died of respiratory failure during the episode of LRI.

All clinical samples were kept on ice and were processed within 2 h. All samples were tested for viral antigen by direct immunofluorescence assays for RSV; PIV-1, -2 or -3; influenza A or B; and adenoviruses. Samples were cultured for viruses and tested by reverse-transcription polymerase chain reaction (RT-PCR) for enterovirus as described elsewhere [5]. BAL samples were processed for bacterial, mycobacterial, and fungal culture and for parasite examination. Aliquots from BAL and NPA samples were stored at −70°C.

NPA and BAL samples were thawed at 37°C, and RNA was extracted by use of the RNeasy kit (Qiagen). RT-PCR was performed in duplicate by use of the OneStep RT-PCR kit (Qiagen). Primers amplified a 170-bp fragment of the L (polymerase) gene that is highly conserved among hMPV isolates [9,13]. Samples were considered to be positive if they were positive in 2 reactions.

Samples were also inoculated onto monolayers of LLC-MK2 cells in OptiMEM medium (Invitrogen) with trypsin and were assessed 3 times weekly. Wells showing cytopathic effects were tested for the presence of hMPV by RT-PCR. Cultures without cytopathic effect were passaged onto fresh cells after 14 days and then incubated for an additional 14 days.

Comparisons of patient- and disease-related variables between virus groups were performed by use of Fisher's exact test. Univariate analyses of the risk factors for progression to LRI were performed by use of Fisher's exact test for discontinuous variables and by Student's *t* test or the Mann-Whitney *U* test for continuous variables. Multivariate analysis of variables predictive of development of an LRI was performed by use of Cox proportional-hazards regression, with the inclusion of variables with $P < .1$ in the prior univariate testing. Age and neutrophil and lymphocyte counts were included as continuous variables and as binary variables (more than or less than a fixed value). The other factors that were analyzed were age, sex, disease group (leukemia/myelodysplasia vs. lymphoid malignancies), disease status (nonadvanced vs. advanced), HSCT (none vs. autologous HSCT vs. allogeneic HSCT), the presence of severe lymphopenia ($<0.2 \times 10^9$ cells/L) or neutropenia ($<0.5 \times 10^9$ cells/L) at the time of virus infection, the development of acute or chronic graft-versus-host disease (GVHD; only for allogeneic HSCT recipients, analyzed as a time-dependent covariable), nosocomial infection, recent use of high-dose corticosteroids (defined as 1 mg/kg of prednisone daily or an equivalent for >1 week), and virus isolated (hMPV vs. other/none). Tests of significance were 2 sided, and $P < .05$ was considered to be statistically significant.

Results

During the 4-year study period, there were 304 separate episodes of respiratory infection that occurred in 128 patients. Results for viruses other than hMPV for patients recruited between October 1999 and May 2001 have been reported elsewhere [5]. The overall male:female ratio was 1.5:1, and the mean age was 49 years (range, 20–72 years). The distribution of underlying diseases is listed in table 1.

Overall, 156 (51%) of 304 of the samples tested positive for a respiratory virus. The number of samples with each virus and sample type is shown in table 1. During the study period, we monitored a total of 494 HSCT recipients (198 allogeneic and 296 autologous) at the medical center. Thus, 112 (23%) of 494 of HSCT recipients had a respiratory virus infection. Two hundred fifty-one samples had remaining aliquots available for hMPV testing. hMPV was detected in 22 (9%) of 251 samples from 22 patients. hMPV was detected in 16 (8%) of 207 NPA samples and in 6 (14%) of 44 BAL samples. The most frequently detected virus was influenza virus, which was found in 68 (22%) of 304 samples from patients with respiratory infections, whereas RSV was detected in 27 (9%) of 304 samples from patients with respiratory infections. There was a community-wide influenza outbreak in 2000 that accounted for 20 of the influenza infections. Fifty-two (17%) of the episodes were coinfections with >1 virus.

Table 1 lists the characteristics of the patients who were infected with hMPV and other viruses. The mean age of patients infected with hMPV was 50 years (range, 23–62 years), which did not differ significantly from that of patients infected with other viruses, and one-half of these patients were male. Seventy-seven percent of the hMPV infections occurred during winter (36%) and spring (41%) months, in contrast to influenza and RSV, which both were most prominent (77% and 78%, respectively) during winter months. There was no year-to-year variability in the number of hMPV infections detected. The infection was considered to be community acquired in 55% and nosocomially acquired in 45% of infections, similar to the proportion of community-acquired versus nosocomial infections for the other viruses (*P*, not significant). Sixteen (73%) of 22 of the hMPV-infected patients were HSCT recipients, who were a mean of 144 days posttransplant (range, 1–488 days), which was not different from the time of onset of all respiratory infections in HSCT recipients (mean, 169 days; range, 3–963 days). There was a trend toward more-advanced underlying disease in the hMPV-infected patients, compared with those infected with influenza virus ($P = .08$) but not compared with those infected with other viruses (*P*, not significant).

The characteristics and outcomes of patients with hMPV and other respiratory virus infections are shown in table 2. hMPV was the primary virus isolated in 18 (82%) of 22 episodes of respiratory infection, whereas, in 4 cases, hMPV infection was detected after infection with another virus had been diagnosed; it was thus considered to be a superinfection. This profile differed only from that of influenza virus, which was the primary viral isolate in 66 (97%) of 68 of respiratory infections ($P = .03$). The majority of patients infected with hMPV presented with URI alone (20/22 [91%]); the rate did not differ significantly from rates in patients infected with other viruses. One patient presented with both URI and LRI, and 1 patient presented with only fever. Nine (41%) of the hMPV-infected patients were coinfected with ⩾1 respiratory virus, as shown in table 2. This frequency was similar to the frequency of coinfection seen with all other viruses except enterovirus ($P = .03$). Sixteen (73%) of 22 of hMPV-infected patients had lymphopenia, whereas only 3 (14%) had neutropenia.

Eight of the hMPV-infected patients who presented with URI alone subsequently progressed to LRI. Thus, 9 (41%) of 22 of the hMPV-infected patients developed LRI. A similar proportion of patients infected with other viruses except rhinovirus presented with or progressed to LRI (*P*, not significant). Three (33%) of hMPV-infected patients with LRI died, 2 of whom had potential bacterial copathogens as determined by BAL *(Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia).* One patient who died had no other viral, fungal, or bacterial pathogens identified. Two of the patients who died were HSCT recipients. All deaths occurred a median of 16 days (range, 3–31 days) after the onset of LRI. Thus, the overall mortality in the hMPV-infected patients was 14% (3/22), which did not differ from that in patients infected with other viruses.

Twenty-nine (23%) of 125 patients who initially presented with URI progressed to LRI, with a median interval between URI and LRI of 9 days (range, 0–32 days). In univariate analysis, risk factors for the progression of URI to LRI included (1) having received an allogeneic HSCT (42% vs. 15%; $P < .001$), (2) having recently received high doses of steroids (40% vs. 20%; $P = .01$), (3) the presence of lymphopenia ($<0.2 \times 10^9$ cells/L) at the onset of infection (60% vs. 18%; $P < .001$), and (4) having RSV (44% vs. 20%) or hMPV (41% vs. 19%) isolated versus any other viruses—influenza A (20%), PIV 1–3 (27%), adenovirus (25%), or picornaviruses (8%) ($P = .02$ for RSV or hMPV vs. others). In multivariate analysis, risk factors were (1) having received an allogeneic HSCT (hazard ratio [HR], 3.2 [95% confidence interval {CI}, 1.1–16.7]; $P = .05$), (2) lymphopenia (HR, 7.8 [95% CI, 2.5–23] $P = .02$), and (3) infection with RSV or hMPV versus other viruses (HR, 4.0 [95% CI, 1.4–11]; $P = .01$).

Discussion

We conducted a prospective study of respiratory virus infections in adult patients with hematologic malignancies, including HSCT recipients. We retrospectively tested samples from these patients and detected hMPV in 9% of acute respiratory infections overall, similar to the frequency of RSV in this cohort. This frequency is comparable to the frequencies of influenza virus, RSV, and PIV infection previously documented in immunocompromised patients [1–5], which suggests that hMPV is also a significant pathogen in this patient population. The winter and spring prominence of hMPV infections reflects the seasonal incidence of hMPV infections described in previous studies [9–13]. A significant number of the hMPV infections appeared to be nosocomial. In the majority of hMPV infections (18/22 [82%]), hMPV was the primary virus isolated, which suggests that it alone was responsible for the associated respiratory illness; overall, 9 (41%) of 22 hMPV-infected patients were coinfected with other viruses.

Patients infected with hMPV had varying degrees of immunosuppression, which suggests that severe immune compromise is not a necessary risk factor for hMPV infection. Similarly, the underlying disease status of hMPV-infected patients did not differ from that of patients infected with other viruses, although there was a trend toward patients with hMPV infection having a more advanced state of underlying disease, compared with patients infected with influenza virus ($P = .08$). There was a high rate of lymphopenia (73%) in the hMPV-infected patients, and 16 (73%) of 22 of these were HSCT recipients. This observation may explain the higher rate of progression of URI to pneumonia found in the multivariate analysis in patients with URI caused by hMPV as opposed to that caused by other viruses (except RSV).

Although the majority of hMPV-infected patients presented with URI alone, 41% of these progressed to LRI; this is comparable to rates of patients with RSV and influenza progressing to LRI in previous studies [1–4]. Of the 9 hMPV-infected patients with LRI, 3 (33%) died, and these deaths were attributable to the LRI. One patient had no other viral, bacterial, or fungal pathogens isolated from BAL samples, which suggests a primary role for hMPV in the death. The other 2 patients had potential bacterial pathogens isolated from BAL sample. Thus, at a minimum, 1 (5%) of 22 hMPV-infected patients—or 1 (11%) of 9 patients with LRIs caused by hMPV—died.

Exact comparisons between the prevalence of hMPV and other viruses in this cohort are difficult to make, because hMPV was detected by a sensitive molecular technique, whereas other viruses (except enterovirus) were detected by a combination of direct immunofluorescence, rapid antigen tests, and culture. A further limitation of the study is the heterogeneity of underlying diagnoses and the degree of immune suppression. Nonetheless, the prospective nature of sample and data collection in the study and the recruitment of patients over a 4-year period provide a unique framework to define the epidemiological and clinical

characteristics of hMPV infection in immunocompromised adults. Our data suggest that hMPV is a significant respiratory pathogen in this population.

References

1. Whimbey E, Champlin R, Couch R, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant patients. Clin Infect Dis 1996;22:778–82. [PubMed: 8722930]
2. Llungman P. Respiratory virus infections in bone marrow transplant patients: the European perspective. Am J Med 1997;102:44–7. [PubMed: 10868142]
3. Bowden RA. Respiratory virus infection after marrow transplant: the Fred Hutchinson Cancer Research Center experience. Am J Med 1997;102:27–30. [PubMed: 10868139]
4. Couch RB, Englund JA, Whimbey E. Respiratory viral infection in immunocompetent and immunocompromised persons. Am J Med 1997;102:2–9. [PubMed: 10868136]
5. Martino R, Rámila E, Rabella N, et al. Respiratory virus infections in adults with hematologic malignancies: a prospective study. Clin Infect Dis 2003;36:1–8. [PubMed: 12491194]
6. Abdallah A, Rowland KE, Schepetiuk SK, To LB, Bardy P. An outbreak of respiratory syncytial virus infection in a bone marrow transplant unit: effect on engraftment and outcome of pneumonia without specific antiviral treatment. Bone Marrow Transplant 2003;32:195–203. [PubMed: 12838285]
7. Jones BL, Clark S, Curran ET, et al. Control of an outbreak of respiratory syncytial virus infection in immunocompromised adults. J Hosp Infect 2000;44:53–7. [PubMed: 10633054]
8. Zambon M, Bull T, Sadler CJ, Goldman JM, Ward KN. Molecular epidemiology of two consecutive outbreaks of parainfluenza 3 in a bone marrow transplant unit. J Clin Microbiol 1998;36:2289–93. [PubMed: 9666007]
9. Van den Hoogen BG, van Doornum GJJ, Fockens JC, et al. Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. J Infect Dis 2003;188:1571–7. [PubMed: 14624384]
10. Boivin G, Abed Y, Pelletier G, et al. Virological features and clinical manifestations associated with human metapneumovirus: a new paramyxovirus responsible for acute respiratory-tract infections in all age groups. J Infect Dis 2002;186:1330–4. [PubMed: 12402203]
11. Esper F, Boucher D, Weibel C, Martinello RA, Kahn JS. Human metapneumovirus infection in the United States: clinical manifestations associated with a newly emerging respiratory infection in children. Pediatrics 2003;111:1407–10. [PubMed: 12777560]
12. Peiris JS, Tang WH, Chan KH, et al. Children with respiratory disease associated with metapneumovirus in Hong Kong. Emerg Infect Dis 2003;9:628–33. [PubMed: 12781000]
13. Williams JV, Harris PA, Tollefson SJ, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. New Engl J Med 2004;350:443–50. [PubMed: 14749452]
14. Cane PA, van den Hoogen BG, Chakrabarti S, Fegan CD, Osterhaus AD. Human metapneumovirus in a haematopoietic stem cell transplant recipient with fatal lower respiratory tract disease. Bone Marrow Transplant 2003;31:309–10. [PubMed: 12621469]
15. Pelletier G, Dery P, Abed Y, Boivin G. Respiratory tract reinfections by the new human metapneumovirus in an immunocompromised child. Emerg Infect Dis 2002;8:976–8. [PubMed: 12194777]

Table 1

Characteristics of patients in the present study of respiratory virus infections in adults with hematologic malignancies, by virus isolated.

Characteristic	Result in patients infected with							Total
	hMPV	Influenza virus	RSV	PIV1 or PIV3	Adenovirus	Rhinovirus	Enterovirus	
No. of episodes positive for a virus/ no. of episodes tested[a]	22/251 (9)	68/304 (22)	27/304 (9)	15/304 (5)	12/304 (4)	3/304 (1)	9/304 (3)	146/304 (48)[b]
Male	11 (50)	42 (62)	15 (55)	10 (67)	7 (58)	1 (34)	8 (89)	94 (60)
Age, median (range), years	50 (23–62)	51 (22–72)	48 (25–72)	48 (21–66)	45 (23–56)	37 (33–40)	45 (20–54)	49 (20–72)
Seasonal occurrence								
Autumn	1 (5)	4 (6)	1 (4)	2 (13)	1 (8)	1	2 (22)	12 (8)
Winter	8 (36)	52 (77)	21 (78)	4 (27)	8 (67)	1	4 (45)	98 (62)
Spring	9 (41)	9 (13)	5 (18)	4 (27)	1 (8)	1	3 (33)	32 (21)
Summer	4 (18)	3 (4)	…	5 (33)	2 (17)	…	…	14 (9
Source of infection								
Community acquired	12 (55)	50 (74)	17 (63)	10 (67)	10 (83)	1	7 (78)	107 (68)
Hospital acquired	10 (45)	18 (26)	10 (37)	5 (33)	2 (17)	2	2 (22)	49 (32)
Underlying disease								
Acute leukemia/ myelodysplastic syndrome	10 (45)	22 (32)	8 (30)	3 (20)	5 (42)	2	2 (22)	52 (33)
Chronic myeloid leukemia	2 (9)	11 (16)	2 (7)	2 (13)	1 (8)	…	…	18 (12)
Chronic lymphocytic leukemia	…	17 (25)	3 (11)	3 (20)	4 (33)	…	3 (33)	30 (19)
Non-Hodgkin lymphoma	2 (9)	…	3 (11)	2 (13)	1 (8)	…	2 (22)	10 (6)
Multiple myeloma	5 (23)	14 (20)	6 (22)	2 (13)	1 (8)	…	2 (22)	30 (19)
Hodgkin disease	3 (14)	2 (3)	5 (19)	2 (13)	…	1	…	13 (8)
Others	…	2 (3)	…	1 (7)	…	…	…	3 (2)
Type of treatment (interval between last chemotherapy and infection)								44 (29)
Chemotherapy (>3 months)	2	13	4	2	2	…	…	23 (7)
Initial chemotherapy (<3 months)	4	5	2	…	…	…	3	14 (11)
Salvage chemotherapy (<3 months)	…	2	…	4	…	…	…	6 (4)
HSCT type								
Autologous	7 (32)	21 (31)	8 (30)	3 (20)	4 (33)	…	3 (33)	46 (31)
Allogeneic	9 (41)	26 (38)	13 (49)	6 (40)	6 (50)	3	3 (33)	66 (45)
Receipt of steroids	2 (9)	13 (19)	4 (15)	3 (20)	3 (24)	2	1 (11)	28 (19)
Status of underlying disease[c]								
Not advanced	10 (45)	40 (68)	16 (59)	8 (53)	8 (66)	1	7 (78)	90 (61)
Advanced	12 (55)	19 (32)	11 (41)	7 (47)	4 (34)	2	2 (22)	57 (39)

NOTE. Data are no. (%) of cases of infection, unless otherwise indicated. BAL, bronchoalveolar lavage; hMPV, human metapneumovirus; HSCT, hematopoietic stem-cell transplantation; LRI, lower respiratory-tract infection; NPA, nasopharyngeal aspirate; PIV, parainfluenza virus; RSV, respiratory syncytial virus; URI, upper respiratory-tract infection.

[a] No. of episodes sampled refers to all episodes of clinically defined URI and/or LRI that were included in a prospective study performed between 1 October 1999 and 31 July 2004, in which NPA and/or BAL samples were tested. Several patients had >1 episode of viral infection during the study period; thus, the no. of distinct episodes (146) is higher than the no. of patients (128).

[b] Nineteen patients had an episode of viral infection in which ≥2 viruses were identified; thus, the actual no. of episodes associated with viral infections was 146, rather than the apparent row total of 156.

[c] Disease phase at transplant was categorized as not advanced (acute leukemia or poor-risk myelodysplasia in first complete remission, untreated good-risk myelodysplasia, first chronic-phase chronic myelogenous leukemia, lymphoid malignancy in first remission, multiple myeloma in first complete or partial response after chemotherapy) or advanced (acute leukemia or myelodysplasia in second

or higher complete remission, relapsed acute leukemia or myelodysplasia, accelerated and blastic-phase chronic myeloid leukemia, lymphoid malignancy in second or higher remission, refractory or relapsed lymphoid malignancy, or any indication for a second transplant).

Table 2

Characteristics of 156 respiratory virus infections, according to initial virus isolated.

Characteristic	Result in patients infected with							Total
	hMPV	Influenza virus	RSV	PIV1 or PIV3	Adenovirus	Rhinovirus	Enterovirus	
No. of infections	22	68	27	15	12	3	9	156
Nature of infection								
Primary viral isolate[a]	18 (82)	66 (97)	18 (67)	14 (93)	8 (67)	2 (67)	9 (100)	135 (87)
Superinfection[b]	4 (18)	2 (3)	9 (33)	1 (7)	4 (33)	1 (33)	…	21 (13)
Clinical presentation[c]								
URI	20 (91)	54 (79)	20 (74)	11 (73)	10 (83)	3 (100)	7 (78)	125 (81)
LRI	…	8 (12)	1 (4)	2 (13)	1 (8)	…	1 (11)	13 (9)
URI + LRI	1 (5)	5 (7)	6 (22)	2 (13)	1 (8)	…	1 (11)	16 (10)
LRI (pneumonia)	9 (41)	20 (29)	11 (41)	6 (40)	5 (42)	0	2 (22)	53 (34)
Initial LRI ± URI	1 (5)	13 (65)	6 (22)	4 (27)	2 (17)	…	2 (22)	28 (18)
URI progressing to LRI	8 (36)	7 (35)	5 (18)	2 (13)	3 (25)	…	…	25 (16)
Neutropenia[d]	3 (14)	8 (12)	4 (15)	3 (20)	4 (33)	1 (33)	…	23 (15)
Lymphopenia[e]	16 (73)	27 (40)	14 (52)	6 (40)	6 (50)	2 (67)	3 (33)	74 (47)
Superinfection by another virus during episode								
RSV	4 (18)[f]	7 (10)	…	…	1 (8)	…	…	12 (8)
Adenovirus	1 (5)	3 (4)	1 (44)	1 (7)	…	…	…	6 (4)
CMV	1 (5)	1 (1)	1 (4)	1 (7)	…	…	…	4 (3)
Influenza A	2 (9)	3 (4)	12 (44)	1 (7)	5 (42)	…	1 (11)	24 (15)
PIV1	…	…	…	…	1 (8)	1 (33)	1 (11)	3 (2)
Enterovirus/rhinovirus	1 (5)	…	…	2 (14)	…	…	…	3 (2)
Respiratory-tract coinfections								
Other respiratory virus	9 (41)[g]	14 (20)	14 (52)	5 (33)	7 (58)	1 (33)	2 (22)	52 (33)
Bacterial	2 (9)	1 (1)	2 (8)	…	…	…		5 (3)
Aspergillus or other fungus	…	2 (3)	…	1 (7)	…	…	…	3 (2)
Death attributed to virus (% of LRI episodes)	3 (33)	4 (20)	3 (27)	2 (33)	2 (40)	0	0	12 (23)
No other copathogens found	1	0	1	2	2	…	…	5
Other copathogens involved	2	4	2	…	…	…	…	6
Invasive aspergillosis	…	1	…	…	…	…	…	1
Gram-negative bacilli	2	1	1	…	…	…	…	4
Cytomegalovirus	…	2	1	…	…	…	…	3

NOTE. Data are no. (%) of cases of infection, unless otherwise indicated. CMV, cytomegalovirus; hMPV, human metapneumovirus; LRI, lower respiratory-tract infection; PIV, parainfluenza virus; RSV, respiratory syncytial virus; URI, upper respiratory-tract infection.

[a] Virus in the column was isolated at beginning of the respiratory illness.

[b] Virus in the column was isolated later in the respiratory illness, after another virus had been isolated.

[c] Two patients presented with fever alone; thus, URI, LRI, and URI + LRI cases total 154.

[d] Neutrophil count, $<0.5 \times 10^9$ cells/L.

[e] Lymphocyte count, $<0.2 \times 10^9$ cells/L.

[f] One case of RSV infection was isolated 2 months after hMPV was detected.

[g] Includes 1 sample that tested positive for CMV, herpes simplex virus, and hMPV.