Human Metapneumovirus Infections in Adults

Another Piece of the Puzzle

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Background: Each winter respiratory viruses account for a significant proportion of serious respiratory illness, including hospitalization, in older adults and those with underlying medical conditions. We describe the incidence and clinical impact of human metapneumovirus (HMPV), a newly identified virus, in adults.

Methods: Infection with HMPV was identified in 3 prospectively enrolled adult cohorts (young persons 19-40 years old, healthy adults ≥65 years old, and high-risk adults) and a hospitalized cohort for 4 consecutive winters (November 15 through April 15 for the years 1999 through 2003). The incidence and clinical impact were compared with those of influenza A and respiratory syncytial virus infection in the same groups.

Results: Using reverse transcriptase–polymerase chain reaction and serologic testing, we identified HMPV infection in 2.2% to 10.5% of the 3 prospectively followed-up outpatient cohorts annually. Asymptomatic infection was common, accounting for at least 38.8% of infections in each of the cohorts. Symptoms, when they occurred, were typical of an upper respiratory tract illness, although a few high-risk persons required hospitalization. Among 1386 hospitalized patients, HMPV was identified in 8.5% (range, 4.4%-13.2%), depending on the year. Dual viral infection was identified in 22.9%. Wheezing was frequent (80%) and more common than with influenza. Twelve percent required intensive care unit admission and 11% ventilatory support, rates similar to those for influenza and respiratory syncytial virus infection.

Conclusions: In adults of all ages, HMPV is a common infection, and, although often asymptomatic, it can result in serious infection that requires hospitalization. Like influenza A and respiratory syncytial virus, HMPV is also a major contributor to the burden of wintertime respiratory illnesses in older adults.
tion during 4 consecutive winters in younger and older adults in inpatient and outpatient settings. Infection was identified in healthy young and elderly persons, frail high-risk adults, and persons hospitalized with acute respiratory symptoms who were prospectively evaluated for respiratory tract infections.

STUDY DESIGN

Infections were identified by analysis of serum and respiratory secretion samples collected from volunteers participating in a study of RSV and influenza infections as previously described, some of whom were also included in the study by Falesy et al. The study encompassed 4 consecutive winters from 1999 through 2003 in Rochester, New York. Four groups were studied: 3 prospective cohorts (young adults 19–40 years old, healthy adults ≥65 years old, and high-risk adults) and a hospitalized cohort. High-risk adults were those with symptomatic lung disease, primarily chronic obstructive pulmonary disease (COPD), or congestive heart failure. The prospective cohorts were enrolled in late summer or early fall and followed up for a maximum of 2 consecutive winters. We used a rolling enrollment scheme to ensure that one-third to one-half of the participants were new each season. On enrollment, demographic, medical history, and functional performance were recorded, a directed respiratory examination was performed, and a serum specimen was collected.

Prospective volunteers notified study personnel of any respiratory symptoms (cough, sore throat, sputum production, nasal congestion, dyspnea, or wheezing) or change in baseline respiratory tract symptoms for high-risk individuals from November 15 through April 15 each winter. Reminders were also mailed every 8 weeks. Illnesses were evaluated by study personnel in the study clinic or during home visits. Evaluation included a directed respiratory tract examination, including measurement of arterial oxygen saturation, and collection of nasal swab and serum samples. Four to 6 weeks later, a convalescent serum specimen was collected at a follow-up visit during which symptom resolution and medical care use were assessed. Postseason blood samples were collected within 6 weeks of completing surveillance.

The hospitalized cohort was recruited from persons with admission diagnoses consistent with an acute cardiopulmonary illness. Eligible participants included those with admission diagnoses of community- or nursing home–acquired pneumonia, acute bronchitis, acute exacerbations of COPD or congestive heart failure, upper respiratory tract illness, viral or influenza syndrome, asthma, or respiratory failure. Patients with acute coronary syndrome, myocardial infarction, or documented pulmonary embolism were excluded. Acute illness and follow-up evaluations were identical to those used for the prospective cohorts, except that hospital records were also reviewed. The University of Rochester Research Subjects Review Board and the Clinical Investigation Committee of Rochester General Hospital approved this study. All participants or their legal guardians signed informed consent before enrollment.

LABORATORY DIAGNOSTICS

Nasopharyngeal swab specimens were stored at −80°C for 3 to 6 years and were then analyzed for HMPV RNA by real-time reverse transcription–polymerase chain reaction (RT-PCR). Conserved forward and reverse primers and a FAM-labeled probe were selected from HMPV N gene sequences available in GenBank (CAN 98–78 strain; AY145284). Briefly, RNA was extracted from 250-µL aliquots of sample using L STAT-50 (Tel-Test, Inc, Friendswood, Texas) according to the manufacturer’s instructions, resuspended in water, and subjected to reverse transcription using a concentration of 200nM of forward primer (5’ CATCGTATATTAAAAGAGTCTCA3’). The resulting RNA was subjected to 42 cycles of PCR (3 seconds at 93°C, 40 seconds at 55°C, and 15 seconds at 68°C) in a thermocycler (iCycler; Bio-Rad, Hercules, California) using the forward primer and reverse primer (5’ TCTGACGATATTTGTAATCAG3’), each at a concentration of 300nM, and a probe (FAM-TGATGAGGGTGTCGTTGTTG-BHQ). The RT-PCR has a sensitivity of 1 plaque-forming unit of virus, using both lineage A and B viruses.

Serologic testing for HMPV was performed using an enzyme immunoassay in which purified virus was used in the solid phase. Briefly, the CAN 97–83 and CAN 98–75 strains (lineage A and B viruses, respectively) were obtained from Gyu Boivin, MD (Laval University, Quebec City, Quebec, Canada), and grown in media that contained 0.1% porcine pancreatic trypsin and 1% albumen on LLC-MK2 monolayers as previously described. After a cytopathic effect was evident, the supernatant was harvested and clarified at low speed for 10 minutes. The viruses were pelleted followed by banding on 60%/30% sucrose gradients. Each purified virus was diluted at equivalent protein concentration in bicarbonate buffer and coated separately overnight on enzyme immunoassay microtiter plates. Serum dilutions were incubated in plates and developed using alkaline phosphatase conjugated goat anti–human IgG followed by substrate. The assay was validated and sensitivity and specificity determined to be 90% (95% confidence interval, 76%–98%) and 99% (95% confidence interval, 92%–100%), respectively, using 111 paired serum samples from patients with previously identified viral infections. These infections included 33 seropositive HMPV infections (defined at the Centers for Disease Control and Prevention by positive serologic test results in all and RT-PCR in 18) and 10 to 12 each of RSV, influenza A, influenza B, coronavirus 229E and OC43, and parainfluenza virus infections. Because identical serologic test results were obtained using either virus alone, presumably from antigenic cross-reactivity between some of the virus proteins, only lineage A virus antigen was used in the study.

LABORATORY DIAGNOSTIC ASSAYS FOR ADDITIONAL RESPIRATORY TRACT VIRUSES

Although the study was initially designed to evaluate RSV and influenza A infections (diagnosed by culture, RT-PCR, and serologic testing), other viruses were also identified either concurrently or retrospectively. These viruses include influenza B (culture and serologic testing), parainfluenza viruses (culture only), adenovirus (culture only), and coronaviruses 229E and OC43 (serologic testing and RT-PCR).

DEFINITION OF INFECTION

Symptomatic HMPV infection was defined as an illness with any upper or lower respiratory tract symptom, but not fever alone, associated with a positive RT-PCR sample collected at the time of symptoms or a 4-fold or higher increase in serum HMPV-specific IgG titer between acute and convalescent serum. Asymptomatic infection was defined as a 4-fold or higher increase in HMPV-specific IgG in serum samples bracketing a time frame in which no illnesses were reported. For example, an increase in titer from preseason to postseason serum samples in persons who did not report an illness during the observation period of November 15 to April 15 was considered evi-
dence of asymptomatic infection. Incompletely evaluated illnesses were those respiratory tract illnesses for which study participants were either out of town or failed to report during the winter but reported to study staff at the final spring interview and demonstrated an increase in HMPV antibody titer. Thus, respiratory samples for RT-PCR were not available for these illnesses, and most did not have tightly bracketed serum samples.

STATISTICAL ANALYSIS

Differences between groups were first analyzed by analysis of variance, and, if significant differences were noted, comparisons between specific groups were calculated using the chi-squared test of independence for dichotomous variables and unpaired, 2-tailed t tests for continuous variables.

RESULTS

POPULATIONS STUDIED

One thousand four hundred thirty-nine persons were enrolled in the prospective cohorts (611 healthy elderly persons, 537 high-risk persons, and 291 young persons) and 1386 hospitalized patients were recruited during the 4 winters of study. The demographic and baseline clinical characteristics of each cohort are given in Table 1. All except the young persons have previously been described in detail. The latter group had a mean age of 33 years, was predominantly female and nonsmokers, and had daily exposure to children. These characteristics differ from those of the healthy elderly group, who had a mean age of 75 years and rarely lived with children, and from the older high-risk group, who had high rates of underlying heart and pulmonary disease. The hospitalized cohort was slightly older and frailer than the high-risk group (reflected by worse functional scores) but was similar in other respects with a high incidence of underlying cardiopulmonary conditions and smoking history.

INCIDENCE OF HMPV INFECTION IN THE PROSPECTIVE COHORTS

The healthy elderly and high-risk persons reported, on average, slightly fewer than 1 illness each and the young cohort reported slightly greater than 1 illness per person during the 2-year period when most were under observation (Table 2). Overall, 36, 49, and 38 HMPV infections were documented by RT-PCR and/or serologic testing in the healthy elderly, high-risk, and young cohorts, respectively. The percentage of study participants under surveillance who were infected with HMPV each year varied considerably, from 2.2% to 10.6%, with the highest number and rate of infections in the second and fourth winters. It was striking that a significant proportion of infections were asymptomatic, detected by serologic testing during intervals when no respiratory illness symptoms were reported. Among the healthy elderly group, 16 of 36 infections (44%) were asymptomatic, whereas 19 of 49 infections (39%) in the high-risk group were asymptomatic. The percentage of asymptomatic infection was greatest in the young group (27 of 38 infections [71%]).

Among study participants with symptomatic infection, in whom both RT-PCR and serologic test results were available, there was evidence of coinfection with other viruses in 26% and 14% of the healthy elderly and high-risk groups, respectively, and in none of the young persons. Coinfecting viruses included influenza A (2 cases; 1 culture positive and 1 seropositive), coronaviruses 229E (5 cases; 2 RT-PCR positive and 3 seropositive), and OC43 (1 case; RT-PCR positive).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Elderly (n=611)</th>
<th>High Risk (n=537)</th>
<th>Young (n=291)</th>
<th>Hospitalized (n=1386)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>75 (6)</td>
<td>70 (11)</td>
<td>33 (5)</td>
<td>75 (12)</td>
</tr>
<tr>
<td>Female, %</td>
<td>57.6</td>
<td>45.6 a</td>
<td>83.8</td>
<td>55.3</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>97.7</td>
<td>93.7</td>
<td>82.1</td>
<td>84.9 a</td>
</tr>
<tr>
<td>Black</td>
<td>2.1</td>
<td>5.4</td>
<td>11.0</td>
<td>9.6</td>
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<tr>
<td>Hispanic</td>
<td>0.2</td>
<td>0.9</td>
<td>5.2</td>
<td>5.5</td>
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<td>Living situation, %</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>25.9</td>
<td>27.4</td>
<td>1.7</td>
<td>28.2</td>
</tr>
<tr>
<td>With adults only</td>
<td>72.0</td>
<td>66.7</td>
<td>10.7</td>
<td>64.4</td>
</tr>
<tr>
<td>With children</td>
<td>2.2</td>
<td>6.0</td>
<td>87.6</td>
<td>7.4</td>
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<tr>
<td>Chronic illnesses, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any cardiac disease</td>
<td>16.5</td>
<td>47.9</td>
<td>0.0</td>
<td>54.6</td>
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<tr>
<td>Lung disease</td>
<td>2.1</td>
<td>64.6</td>
<td>10.0</td>
<td>58.6</td>
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<td>Diabetes mellitus</td>
<td>9.8</td>
<td>16.4</td>
<td>1.4</td>
<td>28.7</td>
</tr>
<tr>
<td>Smoking (current or past), %</td>
<td>55.3</td>
<td>81.9</td>
<td>33.3</td>
<td>73.6</td>
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<td>Influenza vaccine, %</td>
<td>89.6</td>
<td>89.9</td>
<td>38.1</td>
<td>78.1 a</td>
</tr>
<tr>
<td>IADL score, mean (SD)</td>
<td>0.31 (1.1)</td>
<td>1.2 (2.2)</td>
<td>0.03 (0.4)</td>
<td>3.8 (4.1)</td>
</tr>
<tr>
<td>No. of illnesses</td>
<td>525</td>
<td>519</td>
<td>314</td>
<td>1471</td>
</tr>
</tbody>
</table>

Abbreviation: IADL, instrumental activities of daily living.

a Significantly different compared with the other groups of older patients (P < .001).

b Instrumental activities of daily living are functional assessments based on a 12-point scale, with 0 representing total independence and 12, total dependence.
INCIDENCE OF HMPV INFECTION IN HOSPITALIZED PATIENTS

One thousand three hundred eighty-six patients had 1471 hospitalizations evaluated during the 4 winters of study. Overall, 118 HMPV infections were identified, representing 8.5% of the cohort and 8.0% of the illnesses evaluated (Table 2). The yearly incidence varied, paralleling the infection rates noted in the prospective groups, ranging from 4.4% to 13.2% of illnesses each winter. Twenty-seven of the 118 HMPV infections (22.9%) in this group had evidence of dual infection with other viruses, a rate similar to that observed in the elderly and high-risk prospective cohorts. The most frequent coinfecting viruses were RSV (13 patients), coronavirus 229E (6), and influenza A (4).

TEMPORAL DISTRIBUTION OF HMPV INFECTIONS

Human metapneumovirus infections were detected during each of the 4 winters (Figure 1). The number of symptomatic illnesses attributable to HMPV was 23, 62, 34, and 60 during the 4 winters, indicating variable activity from year to year. Infections were detected during most months studied, with heaviest activity in late winter to early spring.
DIAGNOSTIC VIROLOGIC TESTING

Of the 241 HMPV infections identified, 179 were considered symptomatic (50.4% of the prospective and all of the hospitalized infections), of whom 122 (68.2%) had both RT-PCR and tightly bracketed serologic test results available. Of these, 46 (37.7%) were RT-PCR positive and seropositive, 14 (11.5%) were RT-PCR positive and seronegative, and 63 (51.6%) were RT-PCR negative and seropositive. Assuming serologic testing provides the most sensitive assay for HMPV diagnosis, RT-PCR had a sensitivity of 42.2% (46 of 109). Conversely, using RT-PCR as the standard for diagnosis, serologic testing was 78% sensitive (46 of 59), slightly lower than in the validation assessment (see the “Methods” section).

CLINICAL CHARACTERISTICS OF HMPV INFECTION IN PROSPECTIVE COHORTS

To characterize the clinical syndrome associated with HMPV infection in each of the 3 prospective groups, only symptomatic, fully evaluated illnesses not associated with other viruses were analyzed (Table 3). The symptoms were typical of upper respiratory tract virus infection, with most study participants complaining of nasal congestion and cough; rhinorrhea was present in 73.2%. The younger group had significantly more complaints of hoarseness but was less dyspneic than the other groups. Approximately one-third of the healthy elderly and high-risk groups complained of wheezing, although observed wheezing on examination was less common. Although feverishness was reported in 31% to 55%, recorded temperatures were generally normal. The outcome of HMPV infection varied according to group (Table 4). Illness duration ranged from a mean of 10 days in the young group to 16 days in the high-risk group, although some remained ill for as long as 34 days. Utilization of medical care services was greatest in the high-risk group; more than half made a physician office visit, 1 used the emergency department, and 3 were hospitalized during the illness. Treatment primarily consisted of symptom relief, although most high-risk patients and several from the other 2 groups were prescribed antibiotics.

CLINICAL CHARACTERISTICS AND OUTCOME OF HMPV INFECTION IN HOSPITALIZED PATIENTS

The clinical characteristics of the 91 hospitalized patients with HMPV infections (excluding those with dual virus infection) are given in Table 3 and Figure 2. Upper respiratory tract symptoms, such as nasal congestion, were present in approximately half of the patients, although rhinorrhea was rarely observed on examination. Cough was nearly universal, as in the prospective cohorts, and most...
complained of shortness of breath on admission, consistent with a mean room air arterial oxygen saturation of 88.4%. Wheezing was frequent as elicited on history in 80.2% and confirmed on chest examination in an equal number. Half complained of feverishness, although the mean temperature was only 37.8°C. The average symptom duration before hospitalization was 5 days. The most frequent admission diagnoses were acute bronchitis or COPD exacerbation (35 patients [38%]), pneumonia (23 [25%]), and congestive heart failure (14 [15%]). Admission chest radiographs were normal in 34 patients (37%) and showed an infiltrate in 25 (27%). Sputum was obtained in 40 admitted patients (44%) but yielded a pathogen in only 1 patient. Blood cultures were obtained in a similar proportion, with Streptococcus pneumoniae isolated in 1 patient who died. Systemic glucocorticosteroids were administered to 65 patients (71%), bronchodilators to 78 (86%), and antibiotics to 85 (93%). Twelve patients (13%) required intensive care unit care and 11 (12%) ventilatory support. The mean (SD) length of hospitalization in patients with HMPV infection alone was 9 (7) days (range, 2-42 days), and 6 patients (7%) died during or shortly after hospitalization. These 6 averaged 83 years of age, 4 had underlying COPD, and 1 had coronary artery disease and prior stroke. They died between 10 and 30 days after admission, generally of respiratory failure. One patient presented with pneumococcal bacteremia and lobar pneumonia 7 days after the onset of upper respiratory tract symptoms.

**COMMENT**

Even though HMPV was discovered only 6 years ago, a large body of information has already been accumulated about this condition. Published epidemiologic data indicate that it accounts for 5% to 15% of respiratory diseases among hospitalized infants with a clinical syndrome similar to RSV. Like RSV, HMPV induces incomplete immunity, and reinfection later in life is well documented among adults of all ages. Infection has been associated with febrile respiratory illnesses in young and older adults, asthma and COPD exacerbations, and fatal diffuse pneumonia in immunocompromised patients. Although these reports provide information on the clinical spectrum of disease in adults, none present a comprehensive picture of annual attack rates or the full burden of HMPV disease in community-dwelling adults over an extended time. Because most published studies used RT-PCR or culture for diagnosis, the prevalence of asymptomatic or minimally symptomatic infection has not been determined. Thus, we took advantage of a recently completed 4-year prospective study of acute respiratory illness in several large adult cohorts, including approximately 1400 hospitalized persons, to assess the incidence and clinical impact of HMPV infection in this population.

We found that the proportion of the combined prospective cohorts with evidence of HMPV infection varied each winter, ranging from 3.0% to 3.3% in years 1 and 3 to 6.0% to 7.1% in years 2 and 4. The rate of symptomatic infection may have been underestimated in years 3 and 4 because surveillance ended on April 15th when viral activity continued. The variable pattern of virus activity is consistent with the small number of published studies that report HMPV infections during more than a single year. Notably, the incidence of HMPV infection was similar to the 5.5% annual average infection rate for RSV and greater than that of influenza A (2.4%) in these cohorts during the same time frame. The low infection rate for influenza may reflect the high uptake of influenza vaccination. This differs from estimates in infants, in whom the relative activity of HMPV is generally 2- to 3-fold less than that for RSV. This apparent difference in adults may be due to the relatively high frequency of serologically diagnosed asymptomatic or unreported illnesses found in the outpatient cohorts. Although most evident in the young healthy adult, it also was relatively common even among frail elderly patients with underlying cardiopulmonary disease. It is unlikely that the high asymptomatic infection rate resulted from poor specificity of the serologic assay. However, because illness identification required self-reporting, it is possible that some symptomatic illnesses were missed and later forgotten by patients. It is also possible that some illnesses occurred after surveillance ended but before the postseason blood draw, thus misidentifying in-

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Figure 2. Comparison of clinical presentation for human metapneumovirus (HMPV) (n=91), respiratory syncytial virus (RSV) (n=109), and influenza A (n=138) in hospitalized patients, exclusive of mixed viral infections. RSV and influenza data are from Falsey et al. for HMPV compared with influenza A. ICU indicates intensive care unit.
fection as asymptomatic. Nevertheless, HMPV is distinctly different from RSV or influenza A infection in these same populations in which asymptomatic infection is relatively uncommon (approximately \( \leq 10\% \)).\(^2\) Asymptomatic illness has generally not been described in infants, in part because most pediatric studies use RT-PCR evaluation of symptomatic illnesses.\(^11,24,27,28\) A previous study\(^29\) found that randomly selected asymptomatic adults do not have HMPV RNA detectable in their respiratory secretions during the winter. Nevertheless, it appears that mild infection characterized by a serologic response is relatively common. Thus, determining causality with an acute illness solely on the basis of antibody response may be difficult. It is notable that the only description of asymptomatic infection in adults, detected by RT-PCR or culture, is a survey study in severely immunocompromised bone marrow transplant recipients.\(^30\)

Among outpatients, typical upper and lower respiratory tract signs and symptoms characterized illness similar to other winter respiratory viruses. Given the high incidence of asymptomatic infection, one might expect minor symptoms if they occurred. However, when symptoms occurred, illness was not trivial because 38% and 67% of the healthy elderly and high-risk group visited their physicians and one-third of the young adult group called their physicians. Symptoms lasted approximately 2 weeks, and treatment with antipyretics and cough suppressants was frequent. Across all cohorts, use of antibiotics was common, especially among high-risk patients.

The most significant finding is the association of HMPV infection with hospitalization for acute respiratory tract symptoms in adults. During the 4-year period, HMPV infection was identified in 118 of 1471 illnesses (8.0%), 56.1% of which were RT-PCR positive. In comparison, we had previously reported the incidence of influenza A and RSV in this group at 10.5% and 9.6%, respectively.\(^3\) Presenting signs and symptoms were also similar to these other viruses, although, like RSV, wheezing was more common in HMPV infection than influenza A infection (Figure 2). This latter finding is consistent with the similarity of RSV and HMPV in infants in which wheezing is characteristic. The average length of hospitalization for HMPV-infected adults was 9 days, with 13.2% requiring intensive care unit care, and the mortality was slightly less than with influenza A and RSV. Human metapneumovirus infection, similar to RSV, can be mistaken clinically for influenza during winter months when documented influenza circulates.

Of the 118 HMPV infections, co-infection with another virus was noted in 27 (22.9%). Because of the high rate of asymptomatic infection in the outpatient cohorts, it is possible that some patients whose diagnosis was made by serologic testing only may have been hospitalized for reasons other than HMPV infection. Interestingly, a high rate of dual-virus infection also has been reported in infants with HMPV diagnosed by RT-PCR.\(^22,27\) We did not note more severe disease to be associated with the dual infections, as reported by some investigators in infants with RSV-HMPV co-infection.\(^27,28\)

In conclusion, as with other respiratory tract viruses common in childhood, HMPV is a relatively frequent infection in adults of all ages with a wide disease spectrum, ranging from asymptomatic to severe respiratory failure. Overall, HMPV has a substantial impact, although less than that of influenza A and RSV infection, especially in frail older persons with heart or lung disease. Collectively, these 3 viruses were associated with nearly 30% of hospitalizations for acute respiratory illness during the winter. Development of an HMPV vaccine for use in high-risk adults should be considered.

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lence and clinical characteristics of human metapneumovirus infections in hospital-


Correction

Errors in Figures. In the Original Investigation by Chakravarty et al titled “Reduced Disability and Mortality Among Aging Runners: A 21-Year Longitudinal Study,” published in the August 11/25, 2008, issue of the Archives (2008;168[15]:1638-1646), an error occurred in the Figure 2 legend on page 1642. The corrected legend reads as follows: “Figure 2. Mean disability levels by year separated by sex. Solid lines represent data for male participants, and dashed lines represent data for female participants who continued participation through 2005. Only subjects who completed the 21-year follow-up are included. Error bars indicate SD.”

An error also occurred in Figure 1B on page 1641. In the key, the dark dashed line should read “Never runners (completers, n=83)” and the light dashed line should read “Ever runners (completers, n=357).”