MAJOR ARTICLE

Rates of Hospitalizations for Respiratory Syncytial Virus, Human Metapneumovirus, and Influenza Virus in Older Adults

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Background. We performed a prospective study to determine the disease burden of respiratory syncytial virus (RSV) and human metapneumovirus (HMPV) in older adults in comparison with influenza virus.

Methods. During 3 consecutive winters, we enrolled Davidson County (Nashville, TN) residents aged ≥50 years admitted to 1 of 4 hospitals with acute respiratory illness (ARI). Nasal/throat swabs were tested for influenza, RSV, and HMPV with reverse-transcriptase polymerase chain reaction. Hospitalization rates were calculated.

Results. Of 1042 eligible patients, 508 consented to testing. Respiratory syncytial virus was detected in 31 participants (6.1%); HMPV was detected in 23 (4.5%) patients; and influenza was detected in 33 (6.5%) patients. Of those subjects aged ≥65 years, 78% received influenza vaccination. Compared with patients with confirmed influenza, patients with RSV were older and more immunocompromised; patients with HMPV were older, had more cardiovascular disease, were more likely to have received the influenza vaccination, and were less likely to report fever than those with influenza. Over 3 years, average annual rates of hospitalization were 15.01, 9.82, and 11.81 per 10 000 county residents due to RSV, HMPV, and influenza, respectively.

Conclusions. In adults aged ≥50 years, hospitalization rates for RSV and HMPV were similar to those associated with influenza.

Although rates of viral respiratory infections in children are well established, fewer reports exist on the role of viral respiratory infections in respiratory disease in older adults. Respiratory syncytial virus (RSV) is a common virus in childhood, but it also has been reported as a cause of significant morbidity and mortality in the older adult population [1–4]. Rates of adult hospitalization for RSV previously have been estimated using modeling and not based on prospective, population-based, laboratory-confirmed data using sensitive molecular detection methods [2, 5–8]. Human metapneumovirus (HMPV), like RSV, is a paramyxovirus commonly detected in children but also identified in older adults [9, 10]. Little is known about rates of adult hospitalizations due to HMPV. Respiratory syncytial virus and HMPV are challenging to differentiate from influenza in older adults because of the similarity in the clinical presentation of these viruses, their seasonal overlap [10–12], and the difficulty in diagnosis. Rapid antigen tests for RSV and influenza virus have poor sensitivity in older adults, and rapid assays for HMPV are not widely available [13–18]. In addition, RSV and HMPV are difficult to culture [19–21]. Molecular methods offer high sensitivity in adults [19, 22–27] and can accurately detect these viruses as well as influenza virus in older populations [28, 29].

Defining the rates of illness due to RSV and HMPV may support vaccine development for the prevention of disease and drug development for treatment of RSV and HMPV infection. This study was designed to

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establish rates of hospitalizations associated with RSV and HMPV in older adults using sensitive molecular techniques and to compare these rates to the rates of influenza-associated hospitalizations in the setting of high influenza immunization rates [28, 30].

Methods

Study Design

During 3 successive influenza seasons—2006–2007, 2007–2008, and 2008–2009—individuals aged ≥50 years hospitalized with respiratory symptoms or nonlocalizing fever were prospectively enrolled into an ongoing study of influenza vaccine effectiveness in older adults [30]. After informed consent, adult residents of Davidson County (Nashville), Tennessee, were enrolled, as described previously. During the 2006–2007 season, enrollment occurred at 1 academic and 1 community hospital; during the 2007–2008 season, enrollment occurred at 1 academic hospital; and during the 2008–2009 season, enrollment occurred at 1 academic and 3 community hospitals. The number of participating hospitals each year was based on availability of research staff and funding. Recruitment occurred yearly from November through April, based on the circulation of influenza virus. In November, patients were enrolled 2 days a week, and this was increased to 4–5 days per week when influenza virus was identified for2 consecutive weeks in the Vanderbilt University Clinical Laboratory. Davidson County residents aged ≥50 years who were admitted during a 24-hour surveillance period for each enrollment day were eligible if they had any respiratory symptoms (ie, cough, nasal congestion, coryza, dyspnea, or wheezing) or nonlocalizing fever. At the time of consent, nose and throat swabs were obtained and subjects were asked to consent to have specimens stored for future diagnostic studies.

Demographic and Clinical Information

Subjects completed questionnaires, and medical record review captured age, sex, race, medical comorbidities, smoking (self-reported within the past 6 months), use of specific medications (home oxygen, corticosteroids, and immunosuppressants), influenza vaccination status, clinical symptoms, admission to an intensive care unit, endotracheal intubation, length of hospitalization, and status at discharge.

Laboratory Methods

Influenza testing was performed as previously described [30]. Using real-time reverse-transcriptase polymerase chain reaction (RT-PCR), frozen specimens previously evaluated for influenza were tested for RSV using methods published by the Centers for Disease Control and Prevention (CDC) [31] and for HMPV using primers and probes modified from Maertzdorf et al [32 and unpublished data], if the subjects had agreed to additional testing of samples. To insure the quality of the specimens collected, samples were also tested for β-actin (Applied Biosystems) during the 2006–2008 seasons and for RNase P during the 2008–2009 season. If either of the controls were negative in 3 consecutive tests, the RT-PCR results for that specimen were categorized as indeterminate and excluded from the analysis.

Analyses

Only specimens from subjects who gave permission for future testing were included in these analyses. Descriptive analyses were performed using the Fisher exact test for categorical values and logistical regression for continuous variables, using STATA version 9. The numerator for rate calculations was the weighted number of virus-specific hospitalizations. Numbers were weighted to account for number of days of enrollment, proportion of eligible patients enrolled, and the proportion of county respiratory hospitalizations at surveillance hospitals. To determine the proportion of Davidson County residents hospitalized at surveillance hospitals for acute respiratory illness during the surveillance periods, the Hospital Discharge Data System, which receives information from all inpatient discharges from Tennessee hospitals, was used. Denominators for rate calculations were age-specific Davidson County population numbers from the census annual July estimate. We calculated 95% confidence intervals (CIs) for all rates using 1000 bootstrap samples.

RESULTS

Characterization of Enrolled Patients

During the 3-year study period, 1042 Davidson County residents aged ≥50 years and hospitalized with acute respiratory symptoms were identified as eligible for enrollment on surveillance days. Of these, 926 (89%) were approached, and 591 (64%) of these were enrolled (Figure 1). Patients who were not approached included 21% who were discharged or missed,

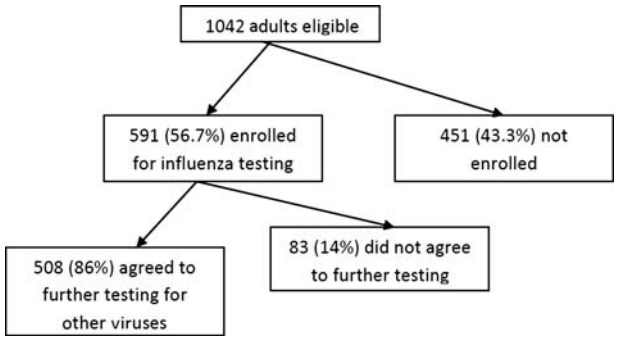

Figure 1. Eligibility and enrollment: 1042 were approached for enrollment, 591 agreed to testing of specimens for influenza alone, and of those 591, 508 agreed to further testing for other viruses.

and 2% who were non-English speaking. Of those approached, reasons for nonenrollment included: patient refusal (26%), surrogate decision maker refusal (4%), physician refusal (<1%), and lack of legal guardian or surrogate decision maker (12%). Those who refused enrollment were significantly older than those enrolled (median age, 73 vs 68; $P = .0001$). Of those enrolled, 508 of 591 patients consented to additional testing of samples. There were no exclusions due to inadequate samples. The 83 subjects who refused further sample testing were older (median age, 71.4 vs 66; $P = .01$) and more likely to be white (87.8% vs 63.6%; $P < .0001$). Enrolled subjects had a median age of 68 years, most lived independently or with family (90.2%), and had ≥1 chronic illness (64.5%) (Table 1). Approximately 71% of subjects had received influenza vaccination for that influenza season, including 78% of those aged ≥65 years.

Clinical Presentation of Specific Viral Infection

The RT-PCR of nasal swab specimens identified 31 (6.1%) of 508 patients with RSV, 23 (4.5%) with HMPV, and 33 (6.5%) with influenza; there were no coinfections. Compared with patients with influenza, patients with RSV were more likely to be aged ≥65 years ($P = .01$) or to be immunocompromised (organ transplant, cancer, splenectomy, human immunodeficiency virus/AIDS, steroids, chemotherapy, immunosuppressive therapy) ($P = .03$). Compared with patients with influenza, patients with HMPV were older ($P = .003$), had more cardiovascular disease ($P = .04$), were less likely to be smokers ($P = .002$), were more likely to have received the influenza vaccination ($P = .006$), and were less likely to report fever ($P = .004$). Gender, race, and living situation (independent or with family) were not associated with specific viral infections. Nearly all patients (78 of 87; 89.7%) infected with 1 of the 3 study viruses had ≥1 medical comorbidity (Table 1).

The median duration of symptoms prior to presentation was 6.5 days with RSV, 5 days with HMPV, and 5 days with influenza. Overall hospital length of stay, admission to and length of stay in the intensive care unit, need for mechanical ventilation, and death were not different among those infected with any of the 3 viruses (Table 2).

Table 1. Characteristics of Enrolled, Tested, and Infected Subjects

Characteristic	Enrolled (n = 591)	Samples Tested for RSV, HMPV, and Influenza (n = 508)	RSV Infection (n = 31/508; 6.1%)	HMPV Infection (n = 23/508; 4.5%)	Influenza Infection (n = 33/508; 6.5%)
Age in years, median (IQR)	68 (58–78.4)	66 (58–78)	68 (56–78)	76.2 (66–83.2)[a]	60 (55–70)
Age group, no. (%)[b]					
50–64 years	254 (43)	226 (44.5)	12 (38.7)	4 (17.4)	23 (69.7)
≥65 years	337 (57)	282 (55.5)	19 (61.3)	19 (82.6)	10 (30.3)
Duration of symptoms in days, median (IQR)	5 (3–8)	5 (3–8)	6.5 (4–7)	5 (4–8)	5 (3–9)
Sex, no. (%)					
Male	239 (40.4)	203 (40)	14 (45.2)	8 (34.8)	9 (27.3)
Female	352 (59. 6)	305 (60)	17 (54.8)	15 (65.2)	24 (72.7)
Race/ethnicity, no. (%)					
White	395 (66.8)	323 (63.6)	22 (71)	14 (60.9)	19 (57.6)
Black	185 (31.3)	175 (34.5)	8 (25.8)	8 (34.8)	14 (42.4)
Living situation, no. (%)					
Independent	154 (26.1)	127 (25)	8 (25.8)	4 (17.4)	4 (12.1)
With family	379 (64.1)	330 (65)	18 (58.1)	16 (69.6)	26 (78.8)
In nursing facility	52 (8.8)	46 (9.1)	4 (12.9)	3 (13)	3 (9.1)
Chronic illnesses, no. (%)					
Cardiovascular disease	351 (59.4)	303 (59.7)	15 (48.4)	18 (78.3)[a]	17 (51.5)
Pulmonary disease	381 (64.5)	322 (63.4)	21 (67.7)	14 (60.9)	23 (69.7)
Diabetes mellitus	234 (39.6)	207 (40.8)	12 (38.7)	7 (30.4)	13 (39.4)
Immunodeficiency[c]	288 (48.7)	241 (47.4)	19 (61.3)[a]	9 (39.1)	11 (33.3)
Smoker (within last 6 months), no. (%)	138 (23.4)	120 (23.6)	8 (25.8)	1 (4.4)[a]	14 (42.4)
Flu vaccination, no. (%)	424 (71.7)	366 (72.1)	20 (64.5)	20 (87)[a]	17 (51.5)

Abbreviations: HMPV, human metapneumovirus; IQR, interquartile range; RSV, respiratory syncytial virus.

[a] Differences were significant ($P < .05$) when compared with influenza virus.

[b] Differences between both RSV and influenza and HMPV and influenza were significant ($P < .05$).

[c] Transplant, cancer, splenectomy, HIV/AIDS, steroid use, chemotherapy, immunosuppression

Table 2. Symptoms at Admission and Clinical Outcomes for Hospitalized Patients with Respiratory Syncytial Virus (RSV), Human Metapneumovirus (HMPV), or Influenza

Characteristic	RSV (n = 31)	HMPV (n = 23)	Influenza Virus (n = 33)
Duration of symptoms in days, median (IQR)	6.5 (4–7)	5 (4–8)	5 (3–9)
Symptoms/signs, no. (%)			
Congestion/ rhinorrhea	25 (80.65)	20 (86.96)	25 (75.76)
Sore throat	19 (61.29)	7 (30.43)	13 (39.39)
Cough	30 (96.77)	23 (100)	32 (96.97)
Dyspnea	27 (87.1)	20 (86.96)	25 (75.76)
Wheezing	25 (80.65)	19 (82.61)	27 (81.82)
Earache	10 (32.26)	3 (13.04)	4 (12.12)
Fever	22 (70.97)	12 (52.17)[a]	29 (87.88)
Nausea/vomiting/ diarrhea	12 (38.71)	10 (43.48)	17 (51.52)
Decreased appetite	19 (61.29)	10 (43.48)	21 (63.64)
Myalgias	12 (38.71)[a]	7 (30.43)[a]	21 (63.64)
Headache	20 (64.52)	9 (39.13)	18 (54.55)
Fatigue	28 (90.32)	19 (82.61)	30 (90.91)
Altered mental status[b]	8/20 (40)	5/10 (50)	6/19 (31.58)
Clinical outcomes			
Length of stay in days, median (IQR)	3 (2–6)	3 (1–4)	4 (2–5)
ICU admission, no. (%)	3 (9.68)	3 (13.04)	2 (6.06)
Length of stay in ICU in days, median (IQR)	5 (3–12)	4 (3–5)	2.5 (1–4)
Mechanical ventilation, no. (%)	1 (3.23)	1 (4.35)	0 (0)
In-hospital death, no. (%)	2 (6.45)	2 (8.7)	0 (0)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] Differences were significant ($P < .05$) when compared with influenza virus.

[b] Not recorded in year one.

Viral-Specific Hospitalization Rates

All 3 viruses circulated during the surveillance period from December through April, with no detection of any of the 3 viruses in November in any of the 3 study seasons (Figure 2). Respiratory syncytial virus peaked in January and February, whereas influenza virus and HMPV peaked in February.

There were no coinfections detected in our cohort. Over the 3-year period studied, average annual rates of hospitalization in adults aged ≥50 years were 15.01, 9.82, and 11.81 per 10 000 residents due to RSV, HMPV, and influenza, respectively (Table 3). For those subjects aged ≥50 years, hospitalization rates for both RSV and HMPV were similar to those for influenza. Rates of hospitalizations for adults aged ≥65 years were higher for HMPV ($P = .05$) than influenza but not statistically different for RSV ($P = .07$) (Table 3).

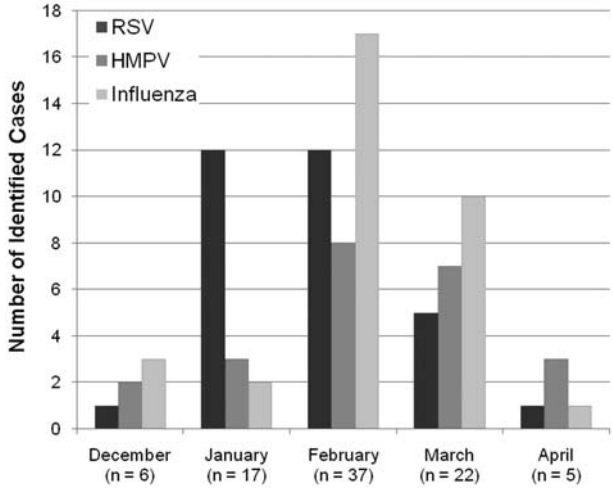

Figure 2. Seasonal variation of virus illness.The timeline of documented infections associated with each of the 3 viruses tested is illustrated. Data from all 3 years are included in this graph.

DISCUSSION

Respiratory syncytial virus and HMPV are well-known pathogens in the pediatric population and are increasingly recognized as significant pathogens in older adults [2, 4, 8, 11, 34–37]. The burden of illness due to RSV is substantial [4]. In 1 prospective study involving 1471 patients hospitalized due to respiratory illness with an average age of 75 years, 9.7% of hospitalizations were due to RSV, and 15% of these required intensive care [4]. In a cohort of adults with both private and government insurance, RSV was estimated to cause 23.4 hospitalizations for pneumonia and influenza per 10 000 person-years in high-risk adults aged ≥65 years [8]. A study of Tennessee nursing home residents enrolled in Medicaid, a government-funded healthcare program for low-income families, estimated that the illness burden of RSV was similar to influenza and accounted for 150 acute respiratory hospitalizations, 760 courses of antibiotics, and 170 deaths per 10 000 nursing home patients annually [2]. In a 9-year study of death certificate data performed by Thompson et al, the mortality rate attributed to RSV-associated respiratory and circulatory illness in persons aged ≥65 years was estimated to be 2.7 per 10 000 person-years [38]. Similar published data are not available for HPMV.

Using prospectively collected data and specimens over 3 years, we determined that RSV and HMPV accounted for 6.1% and 4.5% of hospitalizations for acute respiratory illness during the winter viral respiratory season, respectively. The percentage

Table 3. Weighted Rates of Hospitalization, Adjusting for Number of Days of Enrollment, Proportion of Eligible Patients Enrolled, and the Proportion of County Respiratory Hospitalizations at Surveillance Hospitals

		RSV			HMPV			Influenza Virus		
Age Group	Population	No. of Cases	Weight	Rate/10 000 (95% CI)	No. of Cases	Weight	Rate/10 000 (95% CI)	No. of Cases	Weight	Rate/10 000 (95% CI)
50–64 years	308 329	12	254	8.2 (3.3–12.3)	4	57	1.8 (.3–4.0)	23	356	11.5 (6.8–16.2)
≥65 years	200 711	19	510	25.4 (13.1–38.0)	19	443	22.1 (12.1–33.7)	10	247	12.3 (5.3–21.4)
Overall	509 040	31	764	15.0 (8.6–19.8)	23	500	9.8 (5.8–14.4)	33	603	11.8 (7.6–16.2)

Abbreviations: CI, confidence interval; HMPV, human metapneumovirus; RSV, respiratory syncytial virus.

of hospitalized adults with these 2 respiratory viruses was similar to that which has been previously reported [4, 9, 10, 39].

Because our studies were prospective and population-based rather than based on modeling, we were able to establish laboratory-confirmed hospitalization rates for RSV, HMPV, and influenza. Over the 3-year study period, we found aggregate annual rates of hospitalization to be 15.01, 9.82, and 11.81 per 10 000 residents due to RSV, HMPV, and influenza, respectively. Thus, both RSV and HMPV, as well as influenza, cause a substantial burden of illness in older adults. Our RSV hospitalization rate for adults aged ≥65 years was 25.4 per 10 000. This rate for low- and high-risk patients combined falls between rates reported by Mullooly et al, who used modeling to estimate RSV hospitalization rates to be 10.6 per 10 000 for low-risk patients aged ≥65 years and 44.4 per 10 000 for high-risk patients aged ≥65 years [8]. We found that those individuals infected with influenza were younger than those with either RSV or HMPV and were less likely to be vaccinated. In addition, in those aged ≥65 years, the rate of hospitalizations associated with RSV (rate ratio, 2.06; 95% CI, .8–5.0) and HMPV (rate ratio, 1.79; 95% CI, .8–4.8) was almost double that of hospitalization rates for influenza ($P = .05$, $P = .07$, respectively). This may be due in part to the effectiveness of the influenza vaccine and the relatively high vaccination rates in those aged ≥65 years. In our population, 71% of the enrolled subjects had received influenza vaccination, including 78% of those aged ≥65 years. Our previous work in this population estimated that influenza vaccine was 61% effective in preventing hospitalizations in older adults [30].

Our study has several limitations. We may have underrepresented rates of RSV and HMPV due to the surveillance period being tailored to the circulation of influenza. For example, RSV cases may have been missed due to low surveillance in November, and HMPV may have been missed due to no surveillance into May. Another limitation was our small sample size, making it difficult to draw comparisons of the clinical presentations seen with each virus. A final limitation was that the study only included 1 geographic location, middle Tennessee.

Because both RSV and HMPV can be devastating to the immunocompromised host, the identification of these illnesses in the hospitalized patient could contribute to a reduction of nosocomial spread. Outbreaks in long-term care facilities and assisted living facilities [40–44] suggest that patients with these viral illnesses should be isolated. In a study by Falsey et al, 17% of healthy older adults and close to half of high-risk adults with symptomatic RSV had contact with their healthcare provider (including office visits, emergency room visits, and hospital admissions), and 16% of them were hospitalized [4], providing potentially dangerous exposures to older patients, especially those with weakened immune systems. Currently, the CDC recommends contact precautions in addition to standard precautions when RSV or HMPV are highly suspected or confirmed [45].

Respiratory syncytial virus and HMPV both cause a significant number of hospitalizations in adults aged ≥50 years, especially among those aged ≥65 years. Because their clinical presentation mimics that of influenza, clinical suspicion and sensitive molecular diagnostic methods are needed to detect these infections. In addition, hospitalization rates of RSV and MPV are higher than hospitalization rates of influenza in adults aged ≥65 years, likely due to successful vaccination of the older population in the United States. Antiviral therapy and vaccines for the prevention and treatment of RSV and HMPV should be pursued to reduce the impact of these important viral agents in older adults.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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