Impact of Respiratory Virus Infections on Persons With Chronic Underlying Conditions

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Context While hospitalization rates have declined overall, hospitalizations for acute lower respiratory tract infections have increased steadily since 1980. Development of new approaches for prevention of acute respiratory tract conditions requires studies of the etiologies of infections and quantification of the risk of hospitalization for vulnerable patients.

Objective To determine the frequency of specific virus infections associated with acute respiratory tract conditions leading to hospitalization of chronically ill patients.

Design Analysis of viral etiology of patients hospitalized with acute respiratory tract conditions between July 1991 and June 1995.

Setting Four large clinics and related hospitals serving diverse populations representative of Harris County, Texas.

Patients A total of 1029 patients who were hospitalized for pneumonia, tracheobronchitis, bronchiolitis, croup, exacerbations of asthma or chronic obstructive pulmonary disease, and/or congestive heart failure.

Main Outcome Measure Virus infection, defined by culture, antigen detection, and significant rise in serum antibodies, by underlying condition; hospitalization rates by low- vs middle-income status.

Results Ninety-three percent of patients older than 5 years had a chronic underlying condition; a chronic pulmonary condition was most common. Patients with chronic pulmonary disease from low-income populations were hospitalized at a rate of 398.6 per 10 000, almost 8 times higher than the rate for patients from middle-income groups (52.2 per 10 000; $P<.001$). Of the 403 patients (44.4% of adults and 32.3% of children) who submitted convalescent serum specimens for antibody testing, respiratory tract virus infections were detected in 181 (44.9%). Influenza, parainfluenza, and respiratory syncytial virus (RSV) infections accounted for 75% of all virus infections.

Conclusions Our study suggests that respiratory virus infections commonly trigger serious acute respiratory conditions that result in hospitalization of patients with chronic underlying conditions, highlighting the need for development of effective vaccines for these viruses, especially for parainfluenza and RSV.

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ACUTE RESPIRATORY CONDITIONS are a leading cause of hospitalization of patients with underlying chronic conditions.[1-3] Despite the secular trend for decreasing hospitalization rates overall, the number and rate of hospitalizations for persons with acute lower respiratory tract infections increased steadily during the last 20 years. Almost 1.5 million persons were hospitalized in 1995 after an average increase of more than 28 000 per year since 1980.[1] The hospitalization rate for persons 65 years of age or older with pneumonia increased by 50% from 1985 to 1995.[3] The rates of acute lower respiratory tract infections cited above do not include exacerbations of asthma or chronic obstructive pulmonary disease (COPD). During the same period, the death rate for women with COPD doubled and the hospitalization rate for poor black children with asthma was 4 times greater than that for children from middle-income families.

Recent studies examining the etiology of infections associated with hospitalizations for acute respiratory conditions have focused on elderly patients,[3-5] adults with pneumonia,[6] or persons with asthma.[7-9] These studies showed that influenza virus and respiratory syncytial virus (RSV) were frequently associated with lower respiratory tract illnesses resulting in hospitalization. Recognizing that these conditions are preventable—or potentially preventable—with existing technology, this study was designed to examine comprehensively within a defined population the role of respiratory virus infections in acute respiratory conditions leading to hospitalization of persons of all ages with chronic underlying conditions.

METHODS

Clinical and Epidemiologic Methods

For a 4-year period, July 1991 through June 1995, patients from 4 large clinics were enrolled within 1 day of admission to the hospital. The participating clinics were the Casa de Amigos and Martin Luther King Clinics of the Harris County Hospital District (HCHD) and the Pasadena and West Clinics of Kelsey-Seybold Clinics, all located in

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Harris County, Texas. The Casa de Amigos Clinic serves a low-income, predominantly Hispanic neighborhood, and the Martin Luther King Clinic serves an area populated mainly by low-income blacks. The Pasadena Clinic serves lower middle-income families, most of whom are enrolled in a managed care organization, while the West Clinic is located in a more affluent area and the patients are covered by a variety of insurance plans. A majority of patients at Kelsey-Seybold Clinic and a minority of HCHD patients were from non-Hispanic white ethnic groups.

On each weekday, the lists of admissions for the previous 24 hours to the 3 hospitals—Ben Taub General Hospital, St Luke's Episcopal Hospital, and Texas Children's Hospital—that served the 4 clinics were screened for patients who received their medical care at one of the designated clinics. Patients with an admitting diagnosis suggesting an acute respiratory condition were visited in the hospital to confirm eligibility and to seek consent for participation. Acute respiratory conditions for the purposes of this study were pneumonia, tracheobronchitis, bronchiolitis, croup, exacerbations of asthma or COPD, and congestive heart failure. Patients with active tuberculosis or human immunodeficiency virus (HIV) infection were excluded.

A history of illness was obtained that included immunizations with influenza or pneumococcal vaccine. A combined nasal wash and throat swab specimen for virus culture was obtained within 24 hours of admission to improve isolation of virus. An acute serum specimen also was obtained and patients were scheduled for a convalescent serum specimen about 21 days after admission. After discharge, the medical record was reviewed and the clinical information including the final coded diagnoses was abstracted to a standard form. Virus activity in the community was monitored to provide a guide for the viral antigens to be used in serological tests. To accomplish this, a member of the clinical team visited each clinic for 1 half day each week and obtained cultures from ambulatory patients with acute respiratory illnesses. The results of virus isolation from ambulatory patients for 1991 through 1994 were reported previously.[10]

Populations

The census for the clinics participating in the study was determined by counting the number of active patient records. The proportions with chronic underlying conditions that might put them at risk for complications of respiratory virus infections were determined by reviewing diagnoses recorded in the records. The underlying conditions were the same as those of persons given priority for influenza immunization by the Advisory Committee on Immunization Practices.[11] These include patients aged 65 years or older and those younger than 65 years with cardiopulmonary disorders, metabolic ailments such as diabetes, chronic anemias, chronic renal disease, and malignancies or immunocompromising conditions. Chronic pulmonary conditions were usually asthma for children and young adults and chronic bronchitis and emphysema in older patients. A few of the youngest patients had a diagnosis of bronchopulmonary dysplasia and a few adults had interstitial fibrosis. Computerized patient records were screened for the *International Classification of Diseases, Ninth Revision (ICD-9)* diagnoses that indicated a high-risk condition, and all of the diagnoses for each of the categories listed above were grouped under a unique number and summed for patients with more than 1 type of underlying condition. The unique numbers were as follows: 1, pulmonary; 2, cardiac; 4, renal; 8, diabetes and metabolic; 16, anemias; and 32, malignancy or immunocompromising condition. Therefore, a patient assigned a sum of 3 would have both pulmonary and cardiac conditions; a sum of 9 would indicate a combination of pulmonary disease and diabetes, and so on.

The HCHD assigns patients to clinics by geographic area defined by postal ZIP codes; the codes for Casa de Amigos and Martin Luther King Clinics were used to identify patients for both study and census. All patient encounters at any of the HCHD facilities were surveyed and patients from the 2 clinic areas were counted if they had had a visit during the 1992-1994 period. Age distributions were obtained for all active patients, for the subsets with any high-risk condition, and for those with chronic pulmonary conditions. An active patient had at least 1 medical encounter recorded in the medical record during the period of the surveys. Many subjects had more than 1 high-risk condition; for the purposes of this study, these patients were included in the chronic pulmonary category if this was one of their underlying chronic conditions. Similar counts were obtained for the Pasadena and West Clinics of the Kelsey-Seybold Clinics for the 1994-1995 year. Patients from the Kelsey-Seybold Clinics were identified in the hospital by the name of the admitting physician. The surveys of the later years provided the most complete and accurate censuses for both sets of clinics; these were used to calculate the average annual rates. The study protocol was approved by the Institutional Review Board for Human Studies of Baylor College of Medicine and St Luke's Episcopal Hospital. Hospital and written informed consent was obtained from each patient.

Laboratory Methods

The methods used have been described in previous articles.[12-15] Briefly, respiratory secretion specimens were tested on appropriate tissue cultures (human embryonic lung fibroblasts, HEp-2 cells, primary rhesus monkey kidney, Madin-Darby canine kidney cells, and the LLCMK2 line of rhesus monkey kidney cells) to isolate influenza, parainfluenza, RSV, rhinoviruses, enteroviruses, herpesviruses, and adenoviruses. Standard detection and identification methods were used.

Antibody tests were performed on paired serum specimens by the microneutralization assay for influenza, parainfluenza, RSV, and coronavirus 229E. Hemagglutination-inhibition also was

used to detect influenza antibodies. Enzyme-linked immunosorbent assay (ELISA) was used to measure antibodies to coronavirus OC43[16] and for the fusion protein of RSV.[17] Infection was established by virus isolation, antigen detection (performed by the hospital laboratory), or a significant antibody rise or combinations of these tests. Usually, 2 antigens were used for the prevalent influenza virus—the antigen in the vaccine formula and the antigen for the matching virus type or subtype active during the respiratory disease season in which the illness occurred. Therefore, at least 4 different tests were performed for each prevalent influenza virus. A single 6-fold rise for neutralizing antibody, a single 8-fold rise for the hemagglutination-inhibition test, or a minimum of two 4-fold rises were required to establish an influenza virus infection by antibody rise.[18]

Coronavirus infection was defined as a 4-fold or greater rise in ELISA IgG antibodies or by a 2.5-fold or greater increase that was confirmed on a repeat test.[16] A 4-fold or greater rise defined infection for all other viruses. Dual infections were detected when more than 1 virus was recovered from the same specimen, when a virus isolation was accompanied by a significant antibody rise to a different virus, or significant antibody rises to more than 1 virus occurred. The exception was a rise in antibody to 2 or more parainfluenza viruses; this was considered 1 infection since cross-reactions among the parainfluenza viruses are common. Infection with the parainfluenza virus type most likely to be prevalent at the time of the illness was chosen as the infecting type in these instances. Influenza antibody rises that occurred after vaccination were excluded as evidence of infection.

Statistical Methods

Proportions were compared using the Z test of difference between proportions.[19] Comparison of rates were performed using the Mantel-Haenszel procedure. Statistical significance was set at $P<.05$.

RESULTS

Census for Patients From Clinics Serving Low- and Middle-Income Populations

The census for active patients from the middle-income clinics and low-income clinics along with the proportion with underlying chronic conditions is shown in TABLE 1. The proportion of patients attending the clinics for middle-income patients with high-risk conditions (14.1%) was almost one half of that (25.9%) for patients attending low-income clinics ($P<.001$). Furthermore, patients from the low-income clinics were more likely to have multiple high-risk conditions; 4.5% had more than 1 high-risk condition compared with only 1.1% of patients in middle-income clinics ($P<.001$). This difference was even greater for patients with chronic pulmonary disease; 21.5% of low-income patients with pulmonary disease had at least 1 other high-risk condition compared with only 7.3% of middle-income patients with chronic pulmonary disease ($P<.001$).

Hospitalization Rates for High-Risk Patients

The number of patients hospitalized was adjusted for the fact that patients admitted on Sunday through Thursday only were enrolled in the study. This protocol ensured that all patient specimens would be tested as early as possible to improve recovery of respiratory viruses from secretions. It was assumed that the admission rates were equal for each day of the week so that the numerators used for the calculation of annual rates were 1.4 times the annual average number admitted for each age group. With this adjustment the annual average number of high-risk patients admitted from low-income clinics was 279 compared with only 37 from middle-income clinics; the subsets with chronic pulmonary disease were 195 and 28, respectively.

The hospitalization rate for high-risk low-income patients (311.6 per 10 000) was almost an order of magnitude greater than the rate of 44.7 per 10 000 for high-risk patients in the middle-income population, ($P<.001$). The rates were highest for children younger than 5 years for both populations; low-income school-aged children and elderly middle-income patients also had high hospitalization rates (FIGURE 1). Ninety-three percent of patients older than 5 years had a chronic

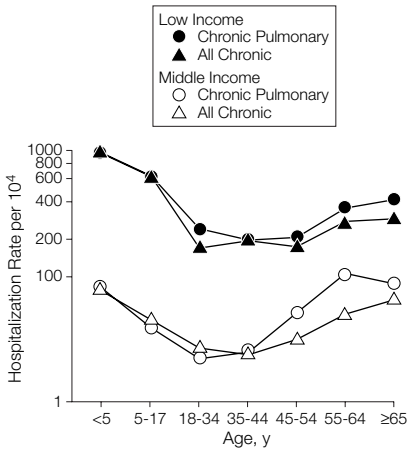
Table 1. Number of Active Patients by Age and Underlying Conditions, Houston, Tex, 1991-1995

	Low-Income Families			Middle-Income Families		
Age, y	No. of Patients	No. (%) With Chronic Conditions	No. (%) With Pulmonary Conditions	No. of Patients	No. (%) With Chronic Conditions	No. (%) With Pulmonary Conditions
<1	1762	120 (6.8)	78 (65.0)	1200	208 (17.3)	180 (86.5)
1-4	3719	453 (12.2)	406 (89.6)	4425	853 (19.3)	812 (95.2)
5-17	5495	773 (14.1)	721 (93.3)	10 201	1356 (13.3)	1265 (93.3)
18-44	11 917	2229 (18.7)	1433 (64.3)	25 955	2373 (9.1)	1684 (71.0)
45-64	8655	3701 (42.8)	1568 (42.4)	12 265	2251 (18.4)	962 (42.7)
≥65	3031	1677 (55.3)	685 (40.8)	4547	1228 (27.0)	462 (37.6)
Total	**34 585***	**8955** (25.9)†	**4892** (54.4)‡	**58 593**	**8269** (14.1)	**5365** (64.9)

*Six with unknown ages.
†Two with unknown ages.
‡One with unknown age.

underlying condition. Most of those hospitalized had chronic pulmonary disease; 65% had been or previously were cigarette smokers—63.5% of adults from the middle-income clinics and 66.1% from low-income clinics. As shown in Figure 1, the hospitalization rate for low-income patients with chronic pulmonary disease was 398.6 per 10 000 compared with 52.2 per 10 000 for patients with chronic pulmonary disease from middle-income families ($P<.001$). Virtually all (96.5%) of the hospitalized patients younger than 35 years from both low- and middle-income clinics had a diagnosis of asthma; older adults had COPD (65.7%), asthma (25.6%), pulmonary fibrosis or sarcoidosis (4.9%), and malignancy or asbestosis (3.9%).

Figure 1. Hospitalization Rates by Age Group for Acute Respiratory Conditions Experienced by Middle- and Low-Income Patients With Chronic Underlying Conditions and for the Subset of Middle- and Low-Income Patients With Chronic Pulmonary Disease



The age-specific rates for middle- and low-income patients were significantly different (all chronic age groups [$P\leq.001$]; chronic pulmonary <5 years, 5-17 years, and 18-34 years [$P<.001$], 35-44 and ≥65 years [$P = .001$], 45-54 years [$P = .02$], and 55-64 years [$P = .02$]).

Association of Virus Infections With Acute Respiratory Conditions

Cultures for respiratory viruses were obtained from a total of 1092 hospitalized patients at the time of 1210 admissions; this total included 118 readmissions. Fourteen patients had positive virus cultures at the time of 2 or more hospital admissions. On 2 occasions, the same virus, RSV and adenovirus, respectively, was recovered from 2 children readmitted after intervals of 21 and 44 days. After review of medical records and final diagnoses of these patients, 1029 admissions for acute respiratory conditions met the criteria for this study. The excluded patients were those with tuberculosis, HIV infection, nonacute respiratory conditions, or those from clinics other than the study clinics. The age distribution of patients at the time of hospital admission is presented in TABLE 2. A total of 415 virus infections were detected among 366 patients; thus, 35.6% of the hospitalized patients had at least 1 virus infection and the proportions for middle-income (37.6%) and low-income (34.3%) patients were similar. Forty-seven had more than 1 virus infection detected; these were reported in a previous publication.[18] Infections with influenza, parainfluenza, and RSV occurred with the predicted seasonal patterns; these are illustrated in an article published in 1996.[10] The combination of culture and antibody tests was available only for these major seasonal viruses. Of 269 infections with RSV, influenza, and parainfluenza viruses, 115 were detected by culture only, 124 by antibody rise only, and 30 by both culture and antibody rise. The availability of paired serum samples was important for detecting infection in adults; 82% of infections were detected by antibody rise compared with 39.6% of infections in children younger than 18 years. Conversely, 69.2% of pediatric infections had positive cultures compared with 31.8% of adult infections.

Although RSV was the most common respiratory virus associated with the acute respiratory conditions surveyed in this study, most (80 of 106) of the RSV infections occurred in children younger than 5 years. Respiratory syncytial virus infection was detected in 25% of children younger than 5 years and in only 3.6% of older subjects ($P<.001$). Influenza virus infections were detected in 85 persons distributed among all age groups. Infections might have been more frequent except for the fact that, of all persons hospitalized, 24.3% of low-income patients and 51.4% of middle-income patients had current influenza immunization. Lower vaccination rates for persons younger than 1 year with proven influenza virus infection—9.1% ($P = .02$) and 25.0% ($P = .05$), respectively—suggest protection by vaccine.

Table 2. Number and Type of Virus Infections Detected in 1029 Patients Hospitalized With Acute Respiratory Conditions, by Age

		Virus Type*												
			Influenza			Parainfluenza								
Age, y	No.	RSV	H3	H1	B	1	2	3	Rhinovirus	Enterovirus	Adenovirus	Coronavirus	HSV	CMV
<1	148	47	4	1	0	2	5	9	10	11	4	2	0	3
1-4	156	33	9	3	2	5	5	9	2	2	2	2	7	2
5-17	139	8	6	4	2	1	1	2	15	2	2	1	4	0
18-44	169	6	14	4	2	6	6	3	7	0	2	7	6	2
45-64	267	10	18	5	3	2	4	9	6	1	2	12	12	0
≥65	150	2	5	1	2	4	4	1	3	1	0	2	9	0
Total	**1029**	**106**	**56**	**18**	**11**	**20**	**25**	**33**	**43**	**17**	**12**	**26**	**38**	**7**

*RSV indicates respiratory syncytial virus; H_3, influenza virus A (H_3 N_2); H_1, influenza virus A (H_1 N_1); HSV, herpes simplex virus; and CMV, cytomegalovirus.
†Percentage with at least 1 virus infection detected.

Parainfluenza virus infections accounted for 78 infections. More than 50% of the parainfluenza virus infections of children younger than 5 years were type 3; the virus types were evenly distributed among older patients. Of 62 picornavirus infections, 42 were isolated from children. Adenoviruses were detected in only 1.2% of the subjects. Coronavirus infections were detected in 3.6% of adult patients; only influenza and parainfluenza viruses were detected more frequently in adults 45 years of age or older. The clinical significance of herpesvirus infections in adults is questionable, but several (9) of the isolates accompanied other virus infections.

A subset of these patients (44.4% of adults and 32.3% of children) submitted convalescent serum specimens for antibody tests. Virus infections were detected in 181 (44.9%) of these 403 patients by virus isolation, antibody rise, or both (TABLE 3). In this subset, at least 1 virus infection was detected in 64% of children younger than 5 years. Infections were detected in 35.1% of school-aged patients, but increased to 47.5% of young adults 18 to 44 years of age. Middle-aged adults, 45 to 64 years of age, had virus infections detected in 40.6% of their illnesses, but the frequency dropped off to about 35% in elderly adults. For adults, the frequency of infection detection was increased by almost 50%—27.8% to 41.5%—by the availability of paired serum specimens.

Infections with influenza, parainfluenza, and RSV were the most commonly detected in the hospitalized patients, comprising about 75% of all virus infections. The association of these viruses with acute respiratory conditions resulting in hospitalization by age group is shown in FIGURE 2. Respiratory syncytial virus predominated in children younger than 5 years and influenza viruses were the most common in patients 5 years of age or older. Parainfluenza viruses were important contributors to illness in all age groups and were more commonly detected than influenza in persons 65 years of age or older.

The frequency of virus infection was virtually the same (42.0%) for high-risk patients as for the total group; 76.9% of the high-risk patients had chronic pulmonary diseases—asthma and COPD—and they also had comparable rates (43.5%) of virus infections. Influenza virus infections were most commonly associated with acute respiratory conditions of hospitalized patients with underlying chronic pulmonary disease; 17.3% of these patients had influenza virus infection compared with 11.5% with parainfluenza virus infections and 10.4% with RSV infections. These 3 virus groups accounted for 74.5% of all virus infections in patients with underlying chronic pulmonary disease. The only other viruses detected with any regularity were coronaviruses (7.3%), despite the fact that adenoviruses and picornaviruses were frequently recovered from ambulatory patients seen in these same clinics during the same period.[10]

Other	Total No. of Virus Infections	No. (%) of Patients With Positive Virus Infections†
0	**98**	85 (57.4)
1 (Rotavirus)	**84**	76 (48.7)
0	**48**	42 (30.2)
2 (Varicella)	**67**	61 (36.1)
0	**84**	73 (27.3)
0	**34**	29 (19.3)
3	**415**	**366** (35.6)

COMMENT

Hospitalization Rates

This investigation focused on hospitalization of high-risk patients with acute respiratory conditions as the most relevant measure of serious outcome. Although death is a frequent outcome in elderly populations, the low mortality rates in younger age groups obscures the serious morbidity revealed by examining age-specific hospitalization rates.[20-22] A wide disparity was observed in the rates of hospitalization for high-risk patients from low-income households compared with those from middle-income groups. Almost three fourths of the patients had chronic pulmonary conditions such as asthma and COPD. Surveys have shown that patients with asthma in low-income groups are less likely to have regular management and are more likely to seek care in hospital clinics and emergency departments, but only when they are in severe respiratory distress frequently resulting in hospitalization.[2,23,24] In addition, persons with limited income have higher rates of smoking and other addictive behaviors that predispose to chronic conditions.[2] Therefore, "low income" designates a subgroup with differences in population characteristics that are complex and not limited to income.

In our study, patients from low-income groups admitted to the hospital were more likely to have multiple high-risk conditions; in fact, 21.5% of persons with chronic pulmonary disease had at least 1 other high-risk condition such as diabetes, hypertension, or cardiac disease compared with only 7.3% from middle-income clinics. The comorbidities increased the likelihood of hospitalization. These factors, combined with crowded living conditions that increase the likelihood of exposure to respiratory viruses[25,26] and environmental pollution,[10,26-29] support an expectation for rates of hospitalization that are higher for chronically ill persons of low-income groups than for middle-income groups.

On the other hand, the rates determined from denominators derived from active patient records could result in a bias toward higher rates in low-income patients because low-income patients who are in remission of symptoms of their chronic illness are less likely to attend the clinic and, therefore, would not be counted in the clinic census that was derived from active charts. Despite this potential bias, the rates for the low-income patients 65 years of age or older were comparable to those reported for elderly COPD patients in Minneapolis, Minn.[30] Ascertainment of cases and denominators for middle-income populations was reasonably complete and accurate.

Respiratory Virus Infections

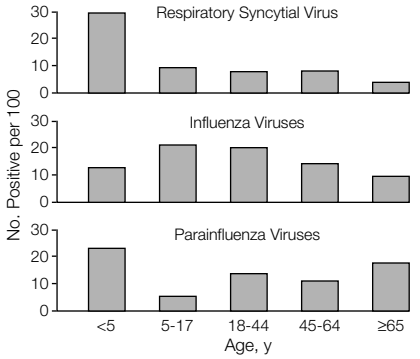
Influenza viruses may cause infections leading to hospitalization for the acute

Table 3. Number and Type of Virus Infections Detected in 403 Patients With Paired Serum Specimens Hospitalized With Acute Respiratory Conditions

		Virus Type*												
			Influenza			Parainfluenza								
Age, y	No. Tested	RSV	H3	H1	B	1	2	3	Rhinovirus	Enterovirus	Adenovirus	Coronavirus	HSV	CMV
<5	86	25	7	3	1	5	9	6	2	4	1	4	2	1
5-17	57	5	6	4	2	1	1	1	3	0	0	1	2	0
18-44	80	6	9	6	1	5	6	0	3	0	0	7	1	1
45-64	128	10	12	4	2	2	4	8	3	1	0	12	6	0
≥65	52	2	3	1	1	4	4	1	0	0	0	2	3	0
Total	**403**	**48**	**37**	**18**	**7**	**17**	**24**	**16**	**11**	**5**	**1**	**26**	**14**	**2**

*RSV indicates respiratory syncytial virus; H_3, influenza virus A (H_3 N_2); H_1, influenza virus A (H_1 N_1); HSV, herpes simplex virus; and CMV, cytomegalovirus.
†Percentage with at least 1 virus infection detected.

Figure 2. Proportions of Patients With Chronic Underlying Conditions Hospitalized for Acute Respiratory Conditions Who Had Infections With Respiratory Syncytial, Influenza, or Parainfluenza Viruses, by Age Group, Houston, Tex, 1991-1995



respiratory conditions defined for this study. This has been substantiated by vaccine effectiveness studies. For example, Nichol et al[6] showed that influenza immunization significantly reduced hospitalizations of elderly patients for pneumonia, exacerbations of chronic pulmonary disease, and congestive heart failure. Moreover, influenza immunization was shown to be cost saving for these high-risk groups. It seems likely that other respiratory viruses have the capacity to trigger severe illnesses in high-risk patients who might also benefit from immunoprophylaxis.

As confirmed by this study, RSV is the most important cause of lower respiratory tract infections leading to hospitalization of children younger than 5 years. The role of RSV as a cause of lower respiratory tract disease in adults is being defined.[4,5] Han et al[3] examined data from the National Hospital Discharge Survey and estimated that between 2% and 9% of hospitalizations and deaths from pneumonia of persons 65 years of age or older are due to RSV. They used published studies of etiology of pneumonia in ambulatory adult populations to estimate national rates.[4,5] Confirming a role for RSV in adults is the documentation of outbreaks in chronic care facilities and the etiology of the often fatal pneumonias in bone marrow transplant patients.[31,32]

Virus infections have been associated with exacerbations of asthma and COPD.[33-39] Studies have defined a role for respiratory viruses including influenza, parainfluenza, RSV, rhinoviruses, and coronaviruses. Smith et al[33] found that only influenza virus infections significantly altered pulmonary function in adults with COPD. The mechanisms for exacerbations of asthma by respiratory virus infection have been studied extensively.[34]

The specific virus infections associated with exacerbations have varied with the age of the subjects and the methods used for virus diagnosis.[35] Many of the older studies have relied on complement fixation, a relatively insensitive test, for antibody detection.[36] This has limited the number of infections detected, particularly in adults in whom diagnosis may depend on a sensitive serological test. Adults have less virus in respiratory secretions than do children, making virus isolation or antigen detection difficult.[37,38] Furthermore, most of the studies have been limited to exacerbations in ambulatory patients, and few have looked at hospitalized patients. In general, the association of virus infections is higher for hospitalized patients, and influenza virus infections are the most common related to the exacerbation.[7,9,39] In our study, 17.3% of hospitalized patients with chronic pulmonary disease had influenza virus infection compared with 11.5% with parainfluenza and 10.4% with RSV infections.

By obtaining cultures for viruses soon after admission and by testing available paired serum specimens with sensitive antibody assays, we were able to associate respiratory virus infections with almost one half of the acute respiratory conditions that resulted in hospitalization. The ability to test for antibody was particularly important for recognizing adult infections. It is likely that more sensitive tests for viral antigens or nucleic acids, such as polymerase chain reaction, could increase further the proportion with virus infection detection.[40]

The role of influenza, and more recently, RSV infection in adult acute respiratory illness, has been recognized, but the important contribution of parainfluenza virus infections seen in this study has not been appreciated. Parainfluenza virus infections occurred more frequently in patients 5 years of age or older than all virus infections except for influenza. Supporting our findings is a recent report from the Ohio Study[5] that associated parainfluenza

Total No. of Virus Infections	No. (%) of Patients With Positive Virus Infections†
70	53 (61.6)
26	20 (35.1)
45	38 (47.5)
64	52 (40.6)
21	18 (34.6)
226	**181** (44.9)

virus infections with 2.5% to 3.1% of adults hospitalized for lower respiratory tract infection during the appropriate seasons.[41]

Efforts to prevent respiratory virus infections should be focused on prevention of the infections that result in hospitalization in high-risk patients. Our studies suggest that vaccines for RSV and parainfluenza viruses should be added to the currently available vaccine for influenza. A subunit vaccine for RSV, purified fusion protein (PFP-2), has had clinical evaluation; Piedra et al[42] demonstrated a beneficial effect of PFP-2 vaccine for children with cystic fibrosis. Effective vaccines for influenza virus, parainfluenza virus, and RSV could potentially reduce hospitalizations of high-risk patients by at least 50%. Developing effective vaccines for these viruses, however, will not be sufficient; improved delivery of vaccines to patients at risk is essential.

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