# Neurological and Neuromuscular Disease as a Risk Factor for Respiratory Failure in Children Hospitalized With Influenza Infection

Ron Keren, MD, MPH

Theoklis E. Zaoutis, MD, MSCE

Carolyn B. Bridges, MD

Guillermo Herrera, MD, MBA

Barbara M. Watson, MBChB

Anna B. Wheeler, MD

Daniel J. Licht, MD

Xian Qun Luan, MS

Susan E. Coffin, MD, MPH

INFLUENZA IS A COMMON DISEASE OF childhood that is responsible for significant morbidity and health care resource utilization, particularly in young children. Healthy young children are hospitalized for influenza-related illness at rates similar to those for elderly persons and adults with chronic medical conditions.[1-4] Influenza also is responsible for substantial seasonal increases in pediatric outpatient visits for respiratory illnesses.[2,4] Perhaps most concerning to parents and physicians, however, is the potential for serious influenza-associated complications, including carditis, encephalitis, myositis, pneumonia, respiratory failure, and death.[5-8]

Population-based studies suggest that individuals with certain chronic medical conditions are at increased risk of serious complications of influenza infection. The Advisory Committee on Immunization Practices (ACIP) has identified 9 groups of chronic medical conditions for which annual influenza vaccination is recommended.[6] They in-

**Context** The Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for children with certain chronic medical conditions to prevent serious complications of influenza infection. Little is known about the relative contribution of each of these chronic medical conditions to the development of serious influenza-associated complications.

**Objective** To identify chronic medical conditions that are associated with respiratory failure in children hospitalized with community-acquired laboratory-confirmed influenza.

**Design, Setting, and Patients** A retrospective cohort study of patients aged 21 years or younger hospitalized at The Children's Hospital of Philadelphia with community-acquired laboratory-confirmed influenza during 4 consecutive influenza seasons (June 2000 through May 2004). We examined 9 ACIP-designated high-risk chronic medical conditions and 3 additional chronic medical conditions (neurological and neuromuscular disease [NNMD], gastroesophageal reflux disease [GERD], and history of prematurity) that in recent studies have been associated with influenza hospitalization and severe influenza-related complications.

**Main Outcome Measures** Rate and odds ratio (OR) of respiratory failure, defined as need for mechanical ventilation.

**Results** Of 745 children hospitalized with community-acquired laboratory-confirmed influenza, 322 (43%) had 1 or more ACIP-designated high-risk chronic medical conditions. Neurological and neuromuscular disease, GERD, and history of prematurity were present in 12%, 14%, and 3%, of children, respectively. Thirty-two children (4.3%) developed respiratory failure. In multivariate logistic regression analyses, conditions associated with respiratory failure included NNMD (OR, 6.0; 95% confidence interval [CI], 2.7-13.5), chronic pulmonary disease other than asthma (OR, 4.8; 95% CI, 1.5-15.1), and cardiac disease (OR, 4.0; 95% CI, 1.6-10.2). The predicted probabilities of respiratory failure derived from the multivariate model were 12% (95% CI, 7%-20%), 9% (95% CI, 3%-23%), and 8% (95% CI, 4%-18%) for children with NNMD, chronic pulmonary disease, and cardiac disease, respectively.

**Conclusions** These results support the ACIP's recent decision to add NNMD to the list of conditions for which annual influenza vaccine is recommended in children. Neurologists and primary care pediatricians should be alerted to the increased risk of respiratory failure and the importance of influenza vaccination in children with NNMD.

*JAMA. 2005;294:2188-2194*                                      www.jama.com

**Author Affiliations:** Division of General Pediatrics, Pediatric Generalist Research Group (Dr Keren), Division of Infectious Diseases (Drs Zaoutis, Wheeler, and Coffin), Division of Neurology (Dr Licht), and Division of Biostatistics and Epidemiology (Mr Luan), Department of Medicine, The Children's Hospital of Philadelphia; Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine (Drs Keren and Zaoutis); Leonard Davis Institute of Health Economics, University of Pennsylvania (Dr Keren); Philadelphia Department of Public Health (Dr Watson), Philadelphia, Pa; and National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Ga (Drs Bridges and Herrera).
**Corresponding Author:** Ron Keren, MD, MPH, Division of General Pediatrics, The Children's Hospital of Philadelphia, 3535 Market St, Room 1524, Philadelphia, PA 19104 (keren@email.chop.edu).

clude asthma, chronic pulmonary disease, cardiac disease, immunosuppression, hemoglobinopathies, chronic renal dysfunction, metabolic and endocrine conditions, long-term salicylate therapy, and pregnancy. Most of the epidemiological studies that identified these chronic conditions as risk factors for serious influenza-related complications were performed in the 1950s and 1960s, focused exclusively on influenza-attributable mortality, and combined children with adults in the analyses.[9-11] More recent studies that have focused exclusively on children confirm that, when considered in combination, these chronic medical conditions are in fact associated with a higher rate of influenza-related complications, as measured by hospitalization, outpatient visits, and antibiotic prescriptions.[4,12,13] However, despite the frequency of influenza infection and the prevalence of these chronic medical conditions,[12,14] little is known about their relative contribution to the development of serious influenza-associated complications. Neuzil et al[12] estimated age-specific complication rates in children with asthma and other respiratory disease but did not have adequate sample size to compare influenza complications in the other high-risk groups. Studies that have used large administrative databases to evaluate the impact of influenza on health outcomes have been limited to estimating hospitalization and mortality rates, and have been unable to accurately evaluate the risk of clinical complications with specific chronic medical conditions.[1-4,15]

In our large retrospective cohort study of children hospitalized with community-acquired laboratory-confirmed influenza during 4 consecutive influenza seasons (2000-2004), we sought to identify chronic medical conditions that were associated with respiratory failure, one of the more common severe influenza complications. In addition to the current ACIP-designated high-risk conditions, we also examined 3 other categories of chronic medical conditions—neurological and neuromuscular disease (NNMD), gas-

troesophageal reflux disease (GERD), and history of prematurity—that in recent studies have been associated with influenza hospitalization[16-18] and severe influenza-related complications.[5]

## METHODS

### Design, Setting, and Patients

We conducted a retrospective cohort study of all patients 21 years or younger hospitalized at The Children's Hospital of Philadelphia (CHOP), Philadelphia, Pa, with laboratory-confirmed influenza infection during 4 consecutive influenza seasons (June 2000 through May 2004). The CHOP is an academic, tertiary care hospital with 418 patient beds and approximately 22 000 hospital admissions each year. To facilitate the appropriate cohorting of patients, it is standard practice at CHOP for patients hospitalized with acute respiratory symptoms of unclear etiology to have a nasal wash specimen obtained for serial testing for respiratory viral pathogens. All specimens are initially tested by enzyme immunoassay for respiratory syncytial virus (Binex, Portland, Me) and influenza (Binex). Direct fluorescent antibody testing for adenovirus, influenza A and B, parainfluenza virus types 1, 2, and 3, and respiratory syncytial virus is performed on specimens that test negative by enzyme immunoassay for respiratory syncytial virus and influenza. Finally, comprehensive viral culture is established for all specimens that are negative for respiratory viruses on direct fluorescent antibody.

Patients hospitalized with laboratory-confirmed influenza were identified in 2 ways. First, we reviewed clinical virology laboratory records from the infection control department to identify hospitalized patients with a positive laboratory test result for influenza A or B. Diagnostic patient specimens included nasal wash or aspirate, tracheal aspirate, bronchoalveolar lavage fluids, or lung tissue obtained by biopsy. We also queried hospital billing data to identify all patients with influenza-specific *International Classification of Diseases, Ninth Revision (ICD-9)* admission or discharge codes (487.0,

487.1, and 487.8). We reviewed all hospital records of patients identified as having influenza by *ICD-9* code but who did not have a positive test result for influenza on review of laboratory records. Patients with no documentation in their medical record of laboratory confirmation of influenza infection were omitted from the final study cohort. Patients who underwent diagnostic testing for influenza at an outside laboratory were retained in the cohort if a physician documented the positive laboratory test result in the CHOP admission note.

### Data Collection

Two research assistants used a structured data collection instrument to retrieve relevant clinical data from the physician admission and discharge notes, laboratory and radiology records, and consultation notes from subspecialists. We also queried electronic hospital billing records to obtain demographic data, such as patient age, sex, race, and ethnicity, and services used, including diagnostic tests, therapies, and physician services. Race and ethnicity were self-reported at the time of hospital registration and recorded by registrars using 4 standardized categories of race and 2 categories of ethnicity. We collected information about race and ethnicity to assess the generalizability of our findings and to determine if the study sample was reflective of the CHOP inpatient population. Billing records also were used to capture clinical data on duration of hospitalization, admission to an intensive care unit, use of mechanical ventilation, radiographic and laboratory diagnostic testing, and medications administered.

### Study Definitions

**Laboratory-Confirmed Influenza.** Laboratory-confirmed influenza infection was defined as a positive determination for influenza A or B virus by rapid assay (enzyme immunoassay or direct fluorescent antibody testing) or comprehensive viral culture.

**Community-Acquired Laboratory-Confirmed Influenza.** Children were

determined to have community-acquired laboratory-confirmed influenza if the first diagnostic specimen positive for influenza was obtained less than 72 hours after hospital admission. If the first positive diagnostic specimen was obtained more than 72 hours after hospitalization, the child was excluded. Children who were admitted with laboratory-confirmed influenza within 72 hours of discharge from a prior hospitalization were presumed to have nosocomial influenza infection and were excluded from this analysis.

**Chronic Medical Conditions.** We used information obtained from detailed review of the hospitalization records (admission note, discharge summary, consultant notes, laboratory and radiological examination reports) to identify children with ACIP-designated high-risk chronic medical conditions, which included asthma, chronic pulmonary disease, cardiac disease, immunosuppression, hemoglobinopathies, chronic renal dysfunction, diabetes mellitus and inborn errors of metabolism, long-term salicylate therapy, and pregnancy. We also identified children with 3 additional chronic medical conditions—NNMD, GERD, and history of prematurity. We used only preexisting conditions described in the hospitalization record in ascribing chronic medical conditions to patients. For example, children who presented to the hospital with a febrile seizure and were found to have influenza were considered to have an NNMD only if they had a prior history of febrile seizures.

### Statistical Analysis

For patients with multiple hospitalizations during the 4-year period, we included only the first hospitalization in the analysis. The dependent variable was respiratory failure, defined as need for mechanical ventilation. The independent variables included the chronic medical conditions outlined above as well as age, sex, race, ethnicity, viral type, and season. We summarized the independent variables, which were all

defined as categorical, using frequencies and percentages. We used univariate and multivariate logistic regression to estimate odds ratios (ORs) for the association between the independent variables and respiratory failure. Because there were only 32 children who developed respiratory failure, we were parsimonious in our selection of independent variables for the multivariate logistic regression, limiting them to variables that were associated with respiratory failure at the $P<.05$ level in univariate analysis.

We used a postestimation command in STATA (Stata Corp, College Station, Tex) to compute adjusted predictions of the probability of respiratory failure for each level (and combination of levels) of the variables in the final multivariate model.

For our primary analysis, seizure disorders were considered an NNMD. A subset of children with NNMD (eg, cerebral palsy) also had a seizure disorder and some children had isolated seizure disorder without another NNMD. We hypothesized that respiratory failure in children with NNMD is related to problems with muscle tone, weakness, and/or aspiration of secretions rather than the presence of a comorbid or isolated seizure disorder. Therefore, in a secondary analysis, we removed seizure disorders from the list of conditions qualifying as an NNMD and included a separate variable for seizure disorder in the analysis.

All statistical calculations were performed using Intercooled STATA version 8 and the institutional review board at CHOP approved the study. Informed consent was not required for this analysis of retrospective data.

## RESULTS
### Characteristics of Children Hospitalized With Community-Acquired Laboratory-Confirmed Influenza

During the 4-year period, we identified 842 hospitalizations for laboratory-confirmed influenza. We excluded 20 repeat hospitalizations, 69 hospitalizations due to nosocomial laboratory-

confirmed influenza, and 8 hospitalizations of patients older than 21 years. The remaining 745 patients hospitalized for community-acquired laboratory-confirmed influenza formed the cohort for subsequent analyses. There were slightly more boys than girls and most of the children (573 [77%]) were younger than 5 years (**TABLE 1**). A total of 408 children (55%) were black and there were few Hispanic children (n=28). A total of 322 patients (43%) had 1 or more chronic medical conditions recognized by the ACIP as risk factors for severe influenza infection. The most prevalent high-risk condition was asthma (24%). In addition, 144 previously healthy children aged 6 to 23 months were hospitalized with community-acquired laboratory-confirmed influenza. Therefore, 466 children (63%) hospitalized with community-acquired laboratory-confirmed influenza were in a group for whom the ACIP previously recommended influenza vaccine (high-risk condition or aged 6-23 months) and 279 children (37%) were not.

A history of prematurity was uncommon (3%) in the total cohort but was present in 11% of infants in the 0- to 5-month age group. Both NNMD and GERD were relatively common, occurring in 12% and 14%, respectively, of children hospitalized with community-acquired laboratory-confirmed influenza. Neurological and neuromuscular disease disorders included central and peripheral nervous system disorders and myopathies (**TABLE 2**). The most common NNMD disorders were cerebral palsy (40%), seizure disorders (42%), and hydrocephalus/cerebrospinal fluid shunt (30%). A total of 41 patients (46%) with an NNMD did not have an ACIP-designated high-risk chronic medical condition and 27 (30%) did not meet ACIP criteria (high-risk condition or aged 6-23 months) for annual influenza vaccination.

### Risk Factors for Respiratory Failure

During the 4-year period, 32 children (4.3%) with community-acquired laboratory-confirmed influenza developed

**Table 1.** Characteristics, Chronic Medical Conditions, and Respiratory Failure in Children Hospitalized With Community-Acquired Laboratory-Confirmed Influenza Infection (N = 745)

| Characteristic | No. of Patients (%) | No. of Patients Within Each Category With Respiratory Failure (%) | Respiratory Failure, OR (95% CI) | |
|---|---|---|---|---|
| | | | Univariate | Multivariate* |
| **Demographics** | | | | |
| Sex | | | | |
|   Male | 436 (59) | 20 (5) | 1.2 (0.6-2.5) | |
|   Female | 309 (41) | 12 (4) | 1.00 | |
| Age group | | | | |
|   0-5 mo | 188 (25) | 3 (2) | 1.00 | |
|   6-23 mo | 250 (34) | 10 (4) | 2.6 (0.7-9.5) | |
|   2-4 y | 135 (18) | 3 (2) | 1.4 (0.3-7.1) | |
|   5-11 y | 92 (12) | 9 (10) | 6.7 (1.8-25.3) | |
|   12-17 y | 53 (7) | 3 (6) | 3.7 (0.7-18.9) | |
|   18-21 y | 27 (4) | 4 (15) | 10.7 (2.2-51.0) | |
| Race† | | | | |
|   White | 249 (34) | 20 (8) | 1.00 | |
|   Black | 408 (55) | 8 (2) | 0.2 (0.1-0.6) | |
|   Asian | 18 (2) | 0 | | |
|   Other | 64 (9) | 4 (6) | 0.8 (0.3-2.3) | |
| Ethnicity† | | | | |
|   Hispanic | 28 (4) | 3 (10) | 2.8 (0.8-9.9) | |
|   Non-Hispanic | 711 (96) | 29 (4) | 1.00 | |
| **Season** | | | | |
| 2000-2001 | 107 (14) | 8 (7) | 1.00 | |
| 2001-2002 | 252 (34) | 6 (2) | 0.3 (0.1-0.9) | |
| 2002-2003 | 135 (18) | 11 (8) | 1.1 (0.4-2.8) | |
| 2003-2004 | 251 (34) | 7 (3) | 0.4 (0.1-1.0) | |
| **Viral type** | | | | |
| Influenza A | 592 (79) | 22 (4) | 0.6 (0.3-1.2) | |
| Influenza B | 154 (21) | 10 (6) | 1.00 | |
| **ACIP high-risk conditions‡** | | | | |
| Asthma | 181 (24) | 11 (6) | 1.7 (0.8-3.5) | |
| Immunosuppressive disorder or therapy | 59 (8) | 4 (7) | 1.7 (0.6-5.0) | |
| Cardiac disease | 52 (7) | 8 (15) | 5.1 (2.2-11.9) | 4.0 (1.6-10.2) |
| Hemoglobinopathy | 41 (6) | 0 | | |
| Chronic pulmonary disease (other than asthma) | 27 (4) | 5 (19) | 5.8 (2.0-16.5) | 4.8 (1.5-15.1) |
| Metabolic disease | 20 (3) | 0 | | |
| Long-term salicylate therapy | 14 (2) | 0 | | |
| Chronic renal dysfunction | 10 (1) | 2 (20) | 5.9 (1.2-28.9) | 3.9 (0.7-20.7) |
| Pregnancy | 0 | 0 | | |
| Any ACIP high-risk condition | 322 (43) | 21 (7) | 2.6 (1.2-5.5) | |
| ≥2 ACIP high-risk conditions | 71 (10) | 8 (11) | 3.4 (1.5-8.0) | |
| **Other conditions§** | | | | |
| NNMD | 89 (12) | 14 (16) | 6.6 (3.2-13.8) | 6.0 (2.7-13.5) |
| GERD | 102 (14) | 11 (11) | 3.6 (1.7-7.7) | 1.2 (0.5-3.0) |
| Prematurity | 23 (3) | 0 | | |

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CI, confidence interval; GERD, gastroesophageal reflux disease; NNMD, neurological and neuromuscular disease; OR, odds ratio.
*Includes only chronic conditions associated with respiratory failure at the *P*<.05 level in univariate analysis.
†Race and ethnicity were self-reported at the time of hospital registration and recorded by registrars using 4 standardized categories of race and 2 categories of ethnicity. Race and ethnicity data were missing for 6 patients (n = 739).
‡Chronic medical conditions that ACIP designates as increasing the risk of influenza-related complications. Patients were classified as having asthma if they received daily asthma controller medications, such as inhaled corticosteroids, cromolyn, and salmeterol, or oral leukotriene receptor antagonists; or if they were older than 24 months and documented to have a history of reactive airway disease or asthma or received daily or episodic bronchodilator medications. Patients were considered immunosuppressed if they had a history of malignancy, collagen vascular disease, primary or acquired immunodeficiency, or received immunosuppressive therapy for more than 2 weeks at the time of hospital admission.
§NNMDs included static or progressive disorders of the central or peripheral nervous system, myopathies, and seizure disorders. Patients were considered to have GERD if they had a documented diagnosis of GERD, jejunal feeding tube, surgical procedure to correct GERD (Nissen fundoplication), or a medication list that included proton pump inhibitors, histamine 2 blockers, or promotility agents. Children younger than 12 months with documented gestational age of less than 37 weeks were considered premature.

**Table 2.** Neurological and Neuromuscular Disease Observed in Cohort

| Disorder | No. of Patients (%)* |
|---|---|
| **Central nervous system disorders** | |
| Cerebral palsy | 36 (40) |
| Hydrocephalus/cerebrospinal fluid shunt | 27 (30) |
| Hypotonia | 6 (7) |
| Stroke | 3 (3) |
| Hypoxic ischemic encephalopathy | 3 (3) |
| Arthrogryposis | 2 (2) |
| Brain cyst | 1 (1) |
| Chiari malformation | 1 (1) |
| Dandy Walker malformation | 1 (1) |
| Heterotopy | 1 (1) |
| Moya Moya disease | 1 (1) |
| Absent corpus collosum | 1 (1) |
| Spina bifida | 1 (1) |
| Mitochondrial disorder | 1 (1) |
| **Neuromuscular diseases** | |
| Spinal muscular atrophy | 4 (4) |
| Becker muscular dystrophy | 1 (1) |
| Duchenne muscular dystrophy | 1 (1) |
| Limb girdle muscular dystrophy | 1 (1) |
| Central nuclear myopathy | 1 (1) |
| **Seizure disorders** | |
| Seizure disorders (unspecified) | 37 (42) |
| Febrile seizures | 14 (16) |
| Infantile spasms | 1 (1) |
| Neonatal seizures | 1 (1) |
| **Peripheral nervous system disorders** | 0 |

Denominator is total number of patients with neurological and neuromuscular disease (n = 89). Sum of percentages is more than 100 because some patients had more than 1 neurological or neuromuscular disease.

respiratory failure as defined by the need for mechanical ventilation. In univariate analyses (Table 1), children aged 5 to 11 years and 18 to 21 years had an increased risk (reference group, children aged 0-5 months) of developing respiratory failure during hospitalization (OR, 6.7; 95% confidence interval [CI], 1.8-25.3; and OR, 10.7; 95% CI, 2.2-51.0, respectively). Black children were less likely than white children to develop respiratory failure (OR, 0.2; 95% CI, 0.1-0.6). Compared with the influenza season in 2000-2001, the risk of respiratory failure was lower in 2001-2002 (OR, 0.3; 95% CI, 0.1-0.9). There were no statistically significant differences in respiratory failure rates across sex and influenza viral type. The ACIP-designated chronic medical conditions that were associated with an increased risk of respiratory failure included, in descending order, chronic renal dysfunction (OR, 5.9; 95% CI, 1.2-28.9), chronic pulmonary disease other

than asthma (OR, 5.8; 95% CI, 2.0-16.5), and cardiac disease (OR, 5.1; 95% CI, 2.2-11.9). Of the non–ACIP-designated chronic conditions, both GERD and NNMD were associated with an increased risk of respiratory failure (OR, 3.6; 95% CI, 1.7-7.7; and OR, 6.6; 95% CI, 3.2-13.8, respectively). None of the children with a history of prematurity developed respiratory failure.

In addition to being a predictor of respiratory failure, being in the oldest age group (18-21 years) also appeared to modify the risk of respiratory failure in patients with NNMD or cardiac disease (OR, 10.5; 95% CI, 0.9-120.0, for both conditions). Although not statistically significant, the OR point estimate for patients aged 18 to 21 years was much greater than the OR estimates for patients younger than 18 years with NNMD (OR, 6.3; 95% CI, 2.9-13.9) or cardiac disease (OR, 2.1; 95% CI, 1.6-10.9).

In multivariate logistic regression, we considered only chronic medical conditions that were associated with respiratory failure in univariate analysis at the *P*<.05 level. These included chronic pulmonary disease other than asthma, chronic renal dysfunction, cardiac disease, GERD, and NNMD. Adjusting for each of these variables simultaneously, chronic pulmonary disease (OR, 4.8; 95% CI, 1.5-15.1), cardiac disease (OR, 4.0; 95% CI, 1.6-10.2), and NNMD (OR, 6.0; 95% CI, 2.7-13.5) remained significantly associated with respiratory failure. These OR estimates remained stable adjusting for age group. The **FIGURE** demonstrates the predicted probability of respiratory failure for children hospitalized with influenza who have various combinations of these 3 chronic conditions. Children with pulmonary disease, cardiac disease, or NNMD had approximately a 10% probability of respiratory failure. Having 2 of the 3 chronic conditions increased the probability another 3- to 4-fold.

Gastroesophageal reflux disease was not significantly associated with respiratory failure in the multivariate model (OR, 1.2; 95% CI, 0.5-3.0) because it was confounded by NNMD. The asso-

ciation of renal dysfunction with respiratory failure lost significance (OR, 3.9; 95% CI, 0.7-20.7) because of the relatively small number of children with renal dysfunction available for multivariate analysis. When we removed seizure disorders from the list of conditions qualifying as an NNMD and defined a new variable for seizure disorder, the risk of respiratory failure for children with NNMD was slightly lower (OR, 5.8; 95% CI, 2.2-14.9), and the risk of respiratory failure for children with a seizure disorder was nonsignificant (OR, 1.5; 95% CI, 0.5-4.5).

Five patients hospitalized with community-acquired laboratory-confirmed influenza died, all of whom developed respiratory failure before death. These included 1 previously healthy 14-month-old child, 2 patients with congenital cardiac disease, 1 patient with static encephalopathy due to severe birth trauma, and 1 former premature infant (>12 months and therefore not considered premature in our analysis).

## COMMENT

In this cohort of children hospitalized with community-acquired laboratory-confirmed influenza, the category of diseases that was independently associated with the highest risk of respiratory failure was NNMD, for which influenza vaccination was not previously recommended. The 2004 ACIP-designated high-risk medical conditions that were most strongly associated with the development of respiratory failure were pulmonary and cardiac disease. Children hospitalized with community-acquired laboratory-confirmed influenza who had 2 of these 3 chronic conditions had a 31% to 39% predicted probability of respiratory failure.

The finding that children with NNMD have an increased risk of respiratory failure when hospitalized with influenza is new but not surprising, given that these children often have compromised pulmonary function and ability to handle secretions, which are further exacerbated in the setting of influenza infection and resultant pneumonias. Our hy-

pothesis that respiratory failure in children with NNMD and influenza infection is due largely to problems with muscle tone, weakness, and handling of secretions rather than seizures was supported by a secondary multivariate analysis in which seizure disorder was not significantly associated with respiratory failure, although NNMD was significantly associated.

Including patients aged 18 to 21 years allowed us to study the effect of influenza infection on adolescents and young adults with chronic diseases of childhood who often receive their care at children's hospitals. Although this age group included the least number of patients, it was associated with the highest rate of respiratory failure (15%; OR, 10.7; 95% CI, 2.2-51.0). This finding can be explained in large part by the high proportion of children in this age group with chronic medical conditions (22 of 27 patients [82%] had an ACIP-designated high-risk medical condition and 2 other patients had an NNMD). Our results, although not statistically significant (likely due to small sample size), also suggest that being in this oldest age group may amplify the effect of NNMD and cardiac disease on the risk of respiratory failure. The finding of effect modification × age likely reflects the medical fragility of patients with these conditions who survive to adolescence and early adulthood.

This is the first study to our knowledge to identify the strong association between the presence of NNMD and the development of respiratory failure among hospitalized children, but not the first to demonstrate that NNMD is relatively common in children hospitalized with community-acquired laboratory-confirmed influenza. In the case series by Vaudry et al[18] of 90 children hospitalized in Alberta with community-acquired laboratory-confirmed influenza, the most common underlying conditions were pulmonary and neurological, which was true in our study as well. Quach et al[17] did not explicitly describe the frequency of underlying neurological conditions in their case series

**Figure.** Predicted Probability of Respiratory Failure in Children With Chronic Medical Conditions Hospitalized With Influenza Infection
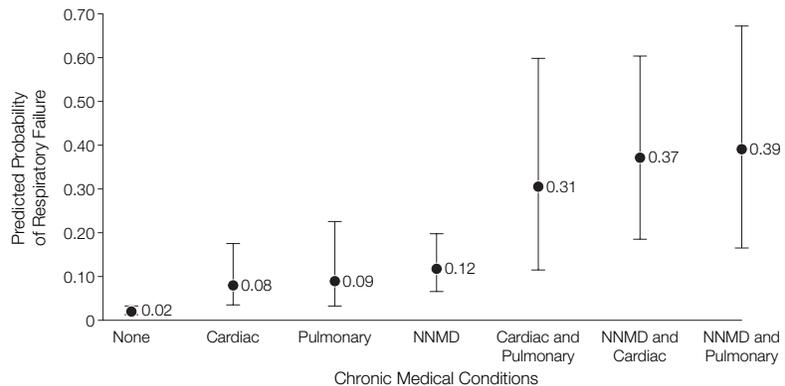


NNMD indicates neurological and neuromuscular disease. None of the patients had all 3 chronic medical conditions. Error bars indicate 95% confidence intervals.

of 182 children hospitalized in Montreal with community-acquired laboratory-confirmed influenza but did report that 9% of admitted children had febrile seizures and 6 patients presented with other neurological manifestations, including new-onset myasthenia gravis and infantile spasms. Interestingly, the overall rate of respiratory failure observed in these smaller studies (4.4% and 5.5%, respectively) was nearly identical to our study (4.4%).

Our study had several limitations. First, the study included patients from only 1 hospital; therefore, the results might not be generalizable to all pediatric inpatient settings, although we suspect that the same results would be found at other large urban children's hospitals. Second, despite the size of the study cohort, we did not have adequate power to identify risk factors for other less common serious influenza complications, such as encephalopathy, carditis, and death. The limited number of children who developed respiratory failure also may have limited our ability to detect weaker associations between certain chronic medical conditions and this outcome. Third, because inclusion was based on hospitalization, we were unable to calculate population-based estimates of risk of respiratory failure; therefore, the results may only be generalizable to other tertiary care children's hospi-

tals. Fourth, we did not know the vaccination status for the majority of the study patients and therefore we could not ascertain the degree to which influenza vaccination may have decreased the likelihood of respiratory failure in children with chronic medical conditions. If influenza vaccination attenuated the severity of illness in children hospitalized with influenza, and children with NNMD had lower vaccination rates than those with chronic medical conditions for which vaccine is currently recommended, the finding of higher rates of respiratory failure in children with NNMD might be partially explained by low vaccination rates in children with NNMD. Finally, it is possible that there was some referral bias, such that the most severely ill children with NNMD were preferentially treated at CHOP instead of local community hospitals when they demonstrated signs and symptoms of influenza. However, for this referral bias to affect our results, it would have to be stronger for children with NNMD than for children with other chronic medical conditions, which is unlikely given the level of specialized care needed to treat children with other chronic conditions.

To our knowledge, our study is the largest reported cohort of children hospitalized with laboratory-confirmed influenza and the only one from a hospital in the United States. Several similar

cohort studies have been performed in Canada,[17,18] Europe,[16] and China,[19] but none had more than 200 patients and therefore were underpowered to evaluate associations between chronic conditions and specific complications. In addition, CHOP's policy of testing all children admitted with respiratory symptoms of unclear etiology and our use of administrative data as a secondary case finding strategy increased the likelihood that we identified most of the influenza cases and reduced the possibility that selection bias was introduced in the assembly of the study sample.

The significantly increased probability of respiratory failure in children with NNMD hospitalized with influenza supports the ACIP's recent decision to add NNMD that may compromise respiratory function to the list of chronic conditions that warrant annual influenza vaccination.[20] Coordinated efforts are needed to educate parents, primary care pediatricians, and pediatric neurologists about the risks of serious influenza complications and the need for annual vaccination for children with NNMD. Future studies should determine the risk of hospitalization among children with NNMD, the number of additional children with NNMD who will require annual vaccination, as well as the effectiveness and cost-effectiveness of the influenza vaccine in preventing hospitalizations and serious complications in these children.

**REFERENCES**

**1.** Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med*. 2000;342:232-239.
**2.** Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med*. 2000;342:225-231.
**3.** Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004;292:1333-1340.
**4.** O'Brien MA, Uyeki TM, Shay DK, et al. Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. *Pediatrics*. 2004; 113:585-593.
**5.** Centers for Disease Control and Prevention. Influenza-associated deaths reported among children aged <18 years—United States, 2003–04 influenza season. *MMWR Morb Mortal Wkly Rep*. 2004;52:1286-1288.
**6.** Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2004;53(RR-6):1-40.
**7.** Connolly AM, Salmon RL, Lervy B, Williams DH. What are the complications of influenza and can they be prevented? experience from the 1989 epidemic of H3N2 influenza A in general practice. *BMJ*. 1993;306: 1452-1454.

**8.** Loughlin J, Poulios N, Napalkov P, Wegmuller Y, Monto AS. A study of influenza and influenza-related complications among children in a large US health insurance plan database. *Pharmacoeconomics*. 2003;21:273-283.
**9.** Collins SDW. *A Review and Study of Illness and Medical Care, With Special Reference to Long-time Trends*. Washington, DC: US Government Printing Office; 1957.
**10.** Collins SDW, Lehmann J. *Excess Deaths From Influenza and Pneumonia and From Important Chronic Diseases During Epidemic Periods, 1918-51*. Washington, DC: US Government Printing Office; 1953.
**11.** Eickhoff TC, Sherman IL, Serfling RE. Observations on excess mortality associated with epidemic influenza. *JAMA*. 1961;176:776-782.
**12.** Neuzil KM, Wright PF, Mitchel EF Jr, Griffin MR. The burden of influenza illness in children with asthma and other chronic medical conditions. *J Pediatr*. 2000; 137:856-864.
**13.** Mullooly JP, Barker WH. Impact of type A influenza on children: a retrospective study. *Am J Public Health*. 1982;72:1008-1016.
**14.** Erhart LM, Rangel MC, Lu PJ, Singleton JA. Prevalence and characteristics of children at increased risk for complications from influenza, United States, 2000. *J Pediatr*. 2004;144:191-195.

**15.** Griffin MR, Coffey CS, Neuzil KM, Mitchel EF Jr, Wright PF, Edwards KM. Winter viruses: influenza- and respiratory syncytial virus-related morbidity in chronic lung disease. *Arch Intern Med*. 2002;162:1229-1236.
**16.** Meury S, Zeller S, Heininger U. Comparison of clinical characteristics of influenza and respiratory syncytial virus infection in hospitalised children and adolescents. *Eur J Pediatr*. 2004;163:359-363.
**17.** Quach C, Piche-Walker L, Platt R, Moore D. Risk factors associated with severe influenza infections in childhood: implication for vaccine strategy. *Pediatrics*. 2003;112:e197-e201.
**18.** Vaudry W, Roth A, Lee B, Spady D. Active surveillance for influenza infection in children: Stollery Children's Hospital, 2003-2004 season. *Can Commun Dis Rep*. 2004;30:157-164.
**19.** Wang YH, Huang YC, Chang LY, et al. Clinical characteristics of children with influenza A virus infection requiring hospitalization. *J Microbiol Immunol Infect*. 2003;36:111-116.
**20.** Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB; Advisory Committee on Immunization Practices (ACIP); Centers for Disease Control and Prevention (CDC). Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2005; 54(RR-8):1-40.