

Risk Factors Associated With Severe Influenza Infections in Childhood: Implication for Vaccine Strategy

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ABSTRACT. Infections caused by influenza virus lead to an excess rate of hospitalization of children during winter months. Current recommendations for vaccination target only children >6 months who belong to specific risk groups.

Objective. To identify possible benefits of universal influenza vaccination, this study aims to determine characteristics of children hospitalized at the Montreal Children's Hospital (MCH) because of an infection attributable to influenza virus as well as risk factors associated with hospitalization.

Methods. We retrospectively reviewed records of all children with a laboratory-proven diagnosis of influenza seen at MCH between April 1, 1999, and April 1, 2002. Data were analyzed using the Student *t* test and logistic regression.

Results. We identified 182 patients hospitalized because of influenza and 114 patients who were not. Admission diagnoses were suspected sepsis (31%), lower respiratory tract infections (27%), and asthma or bronchiolitis (15%). Mean age of hospitalized patients was 26.1 month (median: 12 months), which was similar to that of patients not hospitalized, and 34% were <6 months. Seventy percent of those hospitalized did not have any underlying medical disorder and only 18% (33) were vaccine candidates according to current recommendations. Of the latter, less than half had been vaccinated. Factors associated with hospitalization were age <12 months (odds ratio [OR]: 2.3; 95% confidence interval [CI]: 1.1–4.8), male gender (OR: 1.9; 95% CI: 1.0–3.7), dehydration (OR: 4.3; 95% CI: 1.2–16.0), and decreased oxygen saturation (OR: 32.1; 95% CI: 4.1–249).

Conclusions. Considering that the majority of children hospitalized for influenza do not belong to the specific risk groups targeted by current recommendations, and that one third are <6 months of age, the target population for vaccination needs to be reexamined. Extending vaccination to all young children, to additional high-risk groups, and to pregnant women has potential to reduce the impact of influenza on children. *Pediatrics* 2003;112:e197–e201. URL: <http://www.pediatrics.org/cgi/content/full/112/3/e197;influenza,vaccine,pediatrics,andhospitalization>.

ABBREVIATIONS. MCH, Montreal Children's Hospital; NPA, nasopharyngeal aspirate; DFA, direct immunofluorescent antigen assay; SD, standard deviation; ICU, intensive care unit; IV, intravenous; LOS, length of stay; OR, odds ratio; CI, confidence interval.

Influenza is a common disease of childhood with the highest morbidity occurring in preschool children.^{1–3} Excess hospitalization rates attributable to influenza infections have been estimated to be 104/10 000 child-years for children <6 months of age, 50/10 000 for children between 6 and 12 months of age and 19/10 000 for children between 1 and 3 years of age.⁴ In another study, excess hospitalizations for healthy children <2 years of age was 86 to 112/100 000 child-months,⁵ a rate similar to that reported for adults over 65 years of age.⁶ Higher hospitalization rates are reported for children with underlying high-risk conditions.^{5,7,8} These studies have been criticized because of the difficulty in distinguishing the impact of influenza from that of other respiratory viruses circulating concurrently.⁹ To overcome this problem, a recent study in Hong-Kong used data from one hospital where viral cultures were extensively used to adjust rates for the region. Their yearly excess rates of hospitalization attributable to influenza were 278.5 and 288.2/10 000 children <1 year of age, and 218.4 and 219.3/10 000 children aged between 1 and 2 years in 1998 and 1999, respectively.¹⁰

Less data are available on the impact of laboratory confirmed influenza infections in children. Neuzil and co-workers¹¹ reported a yearly admission rate for proven influenza infections of 3.5/1000 children <2 years of age. In a cohort of infants followed from birth to 12 months of age, most infections and most febrile illnesses as well as lower respiratory tract disease occurred in the second 6 months of life, suggesting that maternal antibody may have been partially protective in the first 6 months.²

Current influenza immunization programs focus on individuals at high risk for influenza-related complications. Pediatric risk groups targeted for immunization include: children with chronic cardiac or pulmonary disorders, children residing in chronic care facilities, and children with chronic conditions such as diabetes mellitus and other metabolic diseases, cancer, immunodeficiency, immunosuppression, renal disease, anemia and hemoglobinopathy.¹² Recently, the American Advisory Committee on Im-

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munization Practices encouraged more widespread use of influenza vaccine among 6- to 23-month-olds and their household contacts for the 2003–2004 season¹³ but Canadian guidelines have not yet included this new risk group in their recommendations.¹²

Currently available influenza vaccine is effective in children but administration is hampered by the need to administer by injection yearly, at a time of many other vaccinations. An attenuated live influenza vaccine that is administered intranasally has been shown to be safe and immunogenic in infants and young children. The overall efficacy of this vaccine in children was 93% against culture-confirmed influenza. Vaccination was also associated with a reduction in the incidence of otitis media with fever.^{14,15} Use of an intranasal vaccine should facilitate more widespread vaccination of children against influenza when it becomes available¹⁶ but so far, the American Food and Drug Administration advisory committee has only recommended its approval for those 5 to 49 years old.¹⁷

To document the burden of illness caused by influenza and to identify groups of children who could benefit from influenza vaccination, we described characteristics of influenza infections in children presenting to the Montreal Children's Hospital (MCH), Quebec, Canada and determined risk factors associated with hospitalization.

METHODS

Study Population

MCH is a 180-bed tertiary care teaching hospital that serves the island of Montreal and surroundings. Children seen in the emergency department with a febrile respiratory illness will usually have a nasopharyngeal aspirate (NPA) for viral culture. Decisions concerning diagnostic tests and admission were at the discretion of the treating physician. Patients with laboratory-confirmed influenza at MCH between April 1, 1999, and April 1, 2002, were identified from the virology laboratory records.

Study Design

Charts of all identified cases were reviewed retrospectively using a standard data collection form. Data collected included date of birth, sex, underlying medical conditions, clinical presentation, investigations performed, laboratory results, treatment, hospitalization at MCH, admission diagnosis, influenza vaccination status if documented. Patients with nosocomial infections (inpatients with signs or symptoms of influenza beginning 3 or more days after admission) that did not result in readmission were analyzed separately. Those hospitalized for reasons unrelated to influenza and those referred for testing only and not evaluated medically at our hospital were excluded. Total admissions and patient-days per 4-week period were obtained from the admissions department of the hospital.

Virology

NPA were routinely tested for influenza A and B virus by direct immunofluorescent antigen assay (IDFA; Chemicon, Chemicon International, Temecula, CA). Specimens were tested on the day they were received and DFA results were available the same day or next morning. NPA testing negative by this assay and specimens collected by throat culture were inoculated into tissue culture (human embryonic lung, A549, rhesus monkey kidney, and Madin-Darby canine kidney cells). Cell lines were examined for a viral cytopathic effect every second day for 16 days. Hemadsorption with washed guinea pig erythrocytes was performed on days 3, 7, 12, and 16. Identification of viruses isolated in cultures was confirmed by DFA. The sensitivity and specificity of DFA was previously assessed in our laboratory and found to be 73.6% and

98.1%, respectively.¹⁸ Specimens were inoculated on the day they were obtained. Subtyping was not routinely done.

Statistical Analysis

Descriptive statistics (mean, standard deviation [SD]), χ^2 tests, and the Student *t* test were used for univariate analyses. Factors associated with admission were analyzed using logistic regression in a stepwise fashion. Multivariate linear regression was used to assess the impact of the method of diagnosis used on the duration of hospitalization and antibiotic use. Variables were kept in the final model if their coefficient was statistically significant, if they confounded variables already present in the model or if they improved significantly the model fit as measured by the log likelihood. All *P* values were considered significant at .05 and were all 2-sided (SAS Institute, version 8.0, Cary, NC).

RESULTS

A total of 330 influenza infections were identified. Of those, 182 cases were hospitalized for influenza, 114 were not hospitalized, and 34 were excluded from the analyses. Exclusions were 21 nosocomial infections, 7 admitted for reasons unrelated to influenza: cardiovascular surgery,² urinary tract infection,² perforated appendicitis,¹ balanitis,¹ and infantile spasms,¹ and 6 referred for testing only and not evaluated medically at our hospital.

Hospitalized Patients

The mean age of the 182 patients hospitalized for influenza was 26.1 months with a SD of 40.3 and a median of 12 months. Sixty-two (34%) were <6 months of age and 70% were <2 years of age. One hundred seven (59%) were male. One hundred twenty-seven (70%) were previously healthy (Fig 1). Of the 55 with underlying illness, 45 were older than 6 months of age and 33 were candidates for influenza vaccination according to current Canadian recommendations.¹² Indications for vaccination were immunocompromised state (12), chronic pulmonary disorders (11), chronic cardiovascular disorders (4), hemoglobinopathies (4), chronic renal failure (1), and child in a chronic care facility (1). Information on influenza vaccination was available in the charts of 14 of these patients and indicated that 8 had not been vaccinated and 6 had experienced vaccine failure. Of the 12 patients with an underlying illness who were not candidates for vaccination, 9 had a chronic neurologic disorder.

The admitting diagnoses were suspected sepsis (31%), lower respiratory tract infection (27%), asthma or bronchiolitis (15%), febrile seizures (9%), dehydration (5%), upper respiratory tract infection (4%) and others (9%). Six patients presented with neurologic manifestation other than febrile seizures: encephalopathy (3), hemibalismus (1), new-onset myasthenia gravis (1), and infantile spasms (1). Presenting symptoms were fever (90%), cough (75%), nasal congestion (73%), anorexia (56%), vomiting (37%), lethargy (33%), and diarrhea (16%). There were no deaths.

Patients were admitted for an average of 5 days (SD: 6.7; median: 3 days). Twenty-one patients (12%) were admitted to the intensive care unit (ICU) and 10 required mechanical ventilation. Among the patients admitted to the ICU, 9 were previously healthy. One hundred twenty-four (69%) received intravenous (IV) antibiotics for a mean duration of 3.8 days (me-

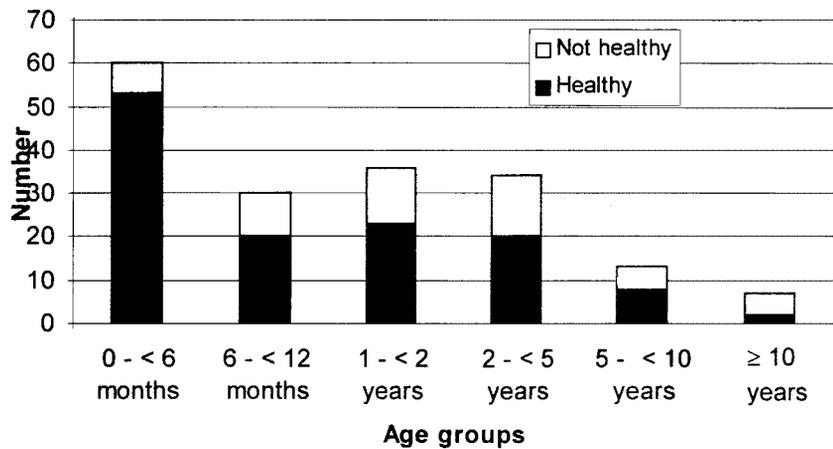


Fig 1. Proportion of previously healthy children admitted for influenza by age group.

dian: 3.0; range: 1–28 days) and 6 patients (3%), all immunocompromised, received antiviral treatment.

There were 143 cases of influenza A (79%) and 39 of influenza B. The diagnosis was made by direct immunofluorescence antigen testing (DFA) in 78%. There was a trend toward shorter length of stay (LOS) for patients when the diagnosis was made by DFA (1.4 day shorter) but this was not statistically significant ($P = .2$). Diagnosis by DFA shortened the duration of IV antibiotic administration by 2.1 day ($P = .014$), using linear regression adjusted for patient's age and days of fever since hospitalization.

Blood cultures were performed in 140 cases (77%) and were positive in only 2: *Streptococcus pneumoniae* in 1 child and *Staphylococcus epidermidis* in a child with a tunnelled central line. Sixty-five children (36%) underwent lumbar punctures. Results were normal in 57, while in the remaining 8, cerebrospinal fluid was contaminated with blood. Chest radiograph was performed in 136 children (75%) and was abnormal (increased markings, infiltrate, collapse) in 89 (65%). Other imaging studies performed included cranial computed tomography in 20, of which 1 showed diffuse cerebral edema, 3 showed preexisting structural abnormalities, and 16 were normal, and cerebral magnetic resonance imaging in 5 (all normal). Electroencephalographic studies were performed in 22 patients and were abnormal in 5. A complete blood count was performed in 162 children. Four children had unexplained thrombocytopenia (platelets $<100\,000/\mu\text{L}$), 10 children had un-

explained neutropenia (neutrophil count $<1000/\mu\text{L}$) while 5 children had a neutrophil count $>15\,000/\mu\text{L}$, and 20 children had a lymphocyte count $<1000/\mu\text{L}$. Transaminases were measured in 18 children and found to be elevated in 5 (28%). Creatinine kinase was elevated in 3 patients (range: 1579–28 806 UI/L).

Five children required readmission within a week of discharge, 3 for progression of their influenza-related disease and 2 with nosocomial rotavirus gastroenteritis.

Hospitalizations because of influenza infections represented 2.2% of all admissions and 1.8% of total patient-days during the months where influenza virus was circulating.

Nosocomial Infections

There were 21 nosocomial infections, 19 febrile upper respiratory tract infections, and 2 cases of pneumonia, one of which required ventilation. Eight of these children were candidates for influenza vaccination. Of 5 with information available, 4 had been vaccinated and 1 had not.

Factors Associated With Hospitalization (Univariate Analysis)

Table 1 compares demographic and clinical characteristics of children hospitalized for influenza and those who were not. Factors that were associated with admission were seizures (odds ratio [OR]: 4.0; 95% confidence interval [CI]: 1.3–11.9), pneumonia (OR: 3.0; 95% CI: 1.0–9.2), dehydration (OR: 3.5; 95%

TABLE 1. Characteristics of Hospitalized and Nonhospitalized Patients

Characteristics	Hospitalized (n = 182) Number (%)	Nonhospitalized (n = 114) Number (%)	OR (95% CI)	P
Decreased oxygen saturation	52 (29%)	2 (2%)	22.6 (5.4–94.8)	
Seizures	23 (13%)	4 (4%)	4.0 (1.3–11.9)	
Dehydration	25 (14%)	5 (4%)	3.5 (1.3–9.4)	
Pneumonia	18 (10%)	4 (4%)	3.0 (1.0–9.2)	
Sex (male)	107 (59%)	54 (47%)	1.6 (1.0–2.6)	
Absolute neutrophil count ($\times 10^9$) mean \pm SD	5.0 \pm 3.9	3.8 \pm 2.5		.01
Nasal congestion	131 (72%)	96 (84%)	0.5 (0.3–0.9)	
Age (<12 mo)	92 (50%)	56 (49%)	1.0 (0.6–1.6)	
Age in months (mean \pm SD)	26.1 \pm 40.3	31.4 \pm 48.8		.25
Underlying medical condition	54 (30%)	30 (26%)	1.2 (0.7–2.0)	
Vaccine candidate	33 (18%)	24 (21%)	0.8 (0.5–1.5)	
Infected with influenza A	143 (79%)	84 (74%)	1.3 (0.7–2.3)	

CI: 1.3–9.4), and decreased oxygen saturation (OR: 22.6; 95% CI: 5.4–94.8). Children with nasal congestion were less likely to be admitted (OR: 0.5; 95% CI: 0.3–0.9).

Presenting symptoms were not significantly different in patients who were hospitalized and in those who were not, with the exception of cough (75% vs 51%), and nasal congestion (73% vs 84%, respectively).

In addition to those listed in Table 1, the following factors were not predictors of hospitalization: diagnosis by DFA (142/182 or 78% of those hospitalized vs 79/114 or 69% of those not hospitalized), lymphocyte count $<1.5 \times 10^9/\text{mm}^3$ (47/155 or 30% of hospitalized vs 15/61 or 25% of nonhospitalized patients), presence of siblings at home (108/138 or 78% of hospitalized vs 31/37 or 84% of patients not hospitalized), number of siblings (mean: 1.0 for hospitalized children vs 1.2 for those not hospitalized), and day care attendance (28/76 or 37% of hospitalized children vs 12/35 or 35% of nonhospitalized). The duration of hospitalization was not influenced by the method of diagnosis of influenza (mean LOS 4.6 days for DFA vs 5.8 days for culture).

Factors Associated With Hospitalization (Multivariate Analysis)

In previous studies,^{4,5} young age was shown to be a risk factor for admission and was forced in the model. The following variables that were significantly associated with the outcome in the univariate analysis were added one at a time. These included: sex, absolute neutrophil count, seizures, pneumonia, dehydration, decreased oxygen saturation, and nasal congestion. The absolute lymphocyte count and presence of an underlying medical condition were also added, as they were perceived to be possible predictors of admission.

In the multivariate logistic regression model, factors associated with admission were age <12 months, male gender, dehydration, decreased oxygen saturation, and nasal congestion (Table 2).

DISCUSSION

Hospitalization for influenza has significant consequences, even for previously healthy children. Among the 127 previously healthy children who were hospitalized, 7% required admission to the ICU. Moreover, the majority of hospitalized patients (69%) received IV antibiotics, three quarters had blood cultures taken and a third underwent lumbar puncture.

As reported previously, children with influenza may be hospitalized for diverse diagnoses such as: suspected sepsis in young infants, lower respiratory

tract infection, exacerbation of asthma, secondary bacterial infections, gastroenteritis, and encephalopathy or febrile seizures.^{19,20} In a study in Hong-Kong, 19.5% of children admitted with influenza A had a febrile seizure, compared with 12.2% admitted with parainfluenza and 9% with adenovirus infections. Repeated seizures were seen more commonly with influenza.²¹ Morishima and colleagues²² have reported an outbreak of encephalitis associated with influenza in Japan, with high rates of mortality and disability. Our study identified only 6 (3.3%) cases of encephalopathy or central nervous system manifestations other than febrile seizures and no case suffered long-term disability.

A patient <12 months of age presenting to the MCH emergency department would have a 2.3-fold increased risk of hospitalization in our hospital, when controlled for other factors. This finding is in keeping with previous studies showing higher admission rates in children <2 years of age.^{8,11,15} Male gender was associated with a nearly 2-fold increase in risk. The high OR for oxygen saturation reflects the seriousness of the condition; 52 of 54 patients (96.3%) with decreased oxygen saturation were hospitalized, while 130 of 242 patients (53.7%) with normal oxygen saturation were hospitalized.

It was expected that underlying medical condition would be a risk factor for admission, as shown previously,^{5,7,8} but it was not. This may be attributable to a selection bias, as children with mild influenza who are healthy may be less likely to be brought for medical attention than children with underlying diseases.

Children with nasal congestion were less likely to be hospitalized. This may be explained by the fact that young infants presenting with fever and no evident focus of infection are more likely to be hospitalized with presumed bacterial sepsis whereas those with signs of upper respiratory tract infection may not be admitted.

Based on 1998 census data and a previous population-based study on the epidemiology of invasive pneumococcal disease,²³ we estimated that the MCH serves 17 257 Montreal children aged <2 years. A total of 56 children aged <2 years and living in Montreal were hospitalized with influenza during the 3-year study period. The incidence of hospitalization for influenza in this age group was therefore estimated to be 108 /100 000 /year, which is in keeping with previous studies.^{4,5,11,24}

Although we may not have identified all children seen in our emergency department who were subsequently hospitalized, as some children may have been admitted to another hospital, we expect this number to be small. Patients who were managed as outpatients often had repeat visits to our emergency department or clinics during their illness.

Considering that the majority of children hospitalized for influenza are previously healthy, the American Advisory Committee on Immunization Practices recommended expanding the groups eligible for influenza vaccine through the Vaccines for Children Program to include children aged 6 to 23 months and their household contacts, starting in the 2003–2004

TABLE 2. Risk Factors Associated With Admission (Multivariate Analysis)

Risk Factors	OR	(95% CI)
Decreased oxygen saturation	32.1	(4.1–249)
Dehydration	4.3	(1.2–16.0)
Age <12 mo	2.3	(1.1–4.8)
Male gender	1.9	(1.0–3.7)
Nasal congestion	0.4	(0.2–0.9)

season.¹³ The American Academy of Pediatrics²⁴ encourages more widespread use of influenza vaccine in young children and their close contacts but presents logistic constraints to universal childhood vaccination using the currently available vaccine. From our data, 100% vaccination coverage of healthy children aged 6 to 23 months could decrease the number of hospitalizations from 182 to 129 (53 children). Additional vaccination of healthy children aged 24 to 59 months could decrease the number to 106, for an overall reduction of >40%.

The high-risk population targeted for vaccination could also be extended to include children with chronic neurologic disorders, identified as an important risk group in our study. However, vaccination rates of currently recognized high-risk children are only 10% to 31%²⁴ and despite vaccine availability, over half of the high-risk children admitted to our hospital with influenza had not been vaccinated. Of the 33 children who were vaccine candidates who were hospitalized, only 6 patients were known to have been vaccinated. The vaccination status of 13 children was not recorded.

One third of our hospitalized children (60 children) were <6 months of age and therefore too young to be vaccinated. For passive protection of this group, vaccination of pregnant women who will be in their second or third trimester during influenza season should be considered.²⁵

In addition to preventing influenza, vaccination has been shown to have an impact on acute otitis media.^{21,22} Vaccination of children aged 1 to 3 years attending day care decreased the rate of otitis media during influenza season by 36% overall and by 83% for otitis media associated with influenza A.²⁶

CONCLUSIONS

Our study showed that the majority of children admitted for influenza did not belong to risk groups for whom yearly vaccination is currently recommended. The impact of influenza on healthy children needs to be recognized. Recommendations that would have most impact on hospitalization in our population would be vaccination of pregnant women, followed by the vaccination of healthy children aged 6 to 23 months, and then, vaccinating healthy children aged 24 to 59 months. Improving compliance with current Canadian recommendations for children with underlying medical conditions and children with chronic neurologic conditions would also be beneficial. With a 100% coverage and a 100% efficacy, these measures would result in a 86% decrease in our hospitalizations for influenza. Universal vaccination of children should become feasible when intranasal influenza vaccine becomes available for young children.

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