BMC
Pediatrics

RESEARCH ARTICLE   **Open Access**

Clinical outcomes of seasonal influenza and pandemic influenza A (H1N1) in pediatric inpatients

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Abstract

Background: In April 2009, a novel influenza A H1N1 (nH1N1) virus emerged and spread rapidly worldwide. News of the pandemic led to a heightened awareness of the consequences of influenza and generally resulted in enhanced infection control practices and strengthened vaccination efforts for both healthcare workers and the general population. Seasonal influenza (SI) illness in the pediatric population has been previously shown to result in significant morbidity, mortality, and substantial hospital resource utilization. Although influenza pandemics have the possibility of resulting in considerable illness, we must not ignore the impact that we can experience annually with SI.

Methods: We compared the outcomes of pediatric patients ≤18 years of age at a large urban hospital with laboratory confirmed influenza and an influenza-like illness (ILI) during the 2009 pandemic and two prior influenza seasons. The primary outcome measure was hospital length of stay (LOS). All variables potentially associated with LOS based on univariable analysis, previous studies, or hypothesized relationships were included in the regression models to ensure adjustment for their effects.

Results: There were 133 pediatric cases of nH1N1 admitted during 2009 and 133 cases of SI admitted during the prior 2 influenza seasons (2007-8 and 2008-9). Thirty-six percent of children with SI and 18% of children with nH1N1 had no preexisting medical conditions (p = 0.14). Children admitted with SI had 1.73 times longer adjusted LOS than children admitted for nH1N1 (95% CI 1.35 - 2.13). There was a trend towards more children with SI requiring mechanical ventilation compared with nH1N1 (16 vs.7, p = 0.08).

Conclusions: This study strengthens the growing body of evidence demonstrating that SI results in significant morbidity in the pediatric population. Pandemic H1N1 received considerable attention with strong media messages urging people to undergo vaccination and encouraging improved infection control efforts. We believe that this attention should become an annual effort for SI. Strong unified messages from health care providers and the media encouraging influenza vaccination will likely prove very useful in averting some of the morbidity related to influenza for future epidemics.

Background

In April 2009, a novel influenza A H1N1 (nH1N1) virus emerged and spread rapidly worldwide. News of the pandemic led to a heightened awareness of the consequences of influenza, as well as some apprehension, in both the general population, the public health sector, and among healthcare providers. Concerns regarding the potential impact of this novel influenza strain led to enhanced infection control practices and strengthened vaccination efforts for both healthcare workers and the general population." [1-5] The media was actively involved in informing the public of the potential consequences of influenza infection and encouraging vigorous vaccination efforts [6].

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Importantly, seasonal influenza (SI) illness in the pediatric population has been previously shown to result in significant morbidity, mortality, as well as substantial hospital resource utilization [7-10]. Although influenza pandemics have the possibility of resulting in considerable illness, we cannot ignore the impact we experience annually with SI. Perhaps the aggressive campaigning and resource allocation reserved for pandemic influenza should be emphasized on an annual basis for SI. We compared the outcomes of a large cohort of pediatric patients admitted for nH1N1 infection to children admitted with SI in the 2007-8 and 2008-9 influenza seasons to determine if there was a significant difference in morbidity. We hypothesized that children admitted with SI would have outcomes including admission to the pediatric intensive care unit, presence of bacterial superinfections, and hospital length of stay (LOS) similar to those admitted with nH1N1.

Methods

Setting
This is a retrospective, cohort study conducted at The Johns Hopkins Children's Medical and Surgical Center (JHCMSC), a part of the Johns Hopkins Hospital (JHH). The JHCMSC is 175-bed pediatric teaching hospital located in Baltimore, Maryland that provides medical care to the Baltimore community and also serves as a tertiary care pediatric hospital for the surrounding region. The hospital admits >8500 children annually, of which >1600 are cared for in the 26-bed pediatric intensive care unit (PICU).

Study Period and Population
We included all children and adolescents 18 years of age and younger admitted to the JHCMSC with a laboratory-confirmed diagnosis of influenza within 24 hours of admission and an influenza-like illness (ILI). An ILI was defined as a fever and upper respiratory tract symptoms (cough, sore throat, rhinorrhea, congestion), lower respiratory symptoms (wheezing, chest pain, shortness of breath), or gastrointestinal symptoms (abdominal pain, vomiting, diarrhea). There were no exclusion criteria. Influenza cases during the 2007-9 seasons that met the inclusion criteria were evaluated. The nH1N1 cases were compared to SI cases.

The Hospital Epidemiology and Infection Control (HEIC) Department has an active surveillance program for respiratory infections among all patients presenting to JHH. http://www.hopkinsmedicine.org/heic/ID/h1n1/index.html. All children with ILI admitted to the JHCMSC are sampled for respiratory viruses. Results are prospectively recorded into the electronic patient medical record and simultaneously supplied to the HEIC computer surveillance system (TheraDoc, Inc, Salt Lake City, UT). One Infection Control Practitioner (AB) queries the system prospectively to identify all patients with positive influenza testing and additional data are abstracted and included in a database. Pediatric cases were identified from the master HEIC database. Medical records were reviewed and demographic, laboratory, radiographic, and clinical data were collected onto standardized case report forms. Patients were identified as having bacterial pneumonia based on previously described criteria including radiographic evidence of a new infiltrate [11].

Laboratory Methods
All respiratory virus samples were collected via nasopharyngeal aspirate (NPA) by trained nursing staff. Respiratory virus testing from May-December 2009 consisted of direct fluorescent antibody (DFA) assay (D^3, Diagnostic Hybrids Inc.[DHI], Athens, OH). Shell vial (R-Mix Too, DHI) and conventional tube cultures (rhesus monkey kidney and A549 cells, Diagnostic Hybrids, Inc.) were inoculated in parallel with DFA for all samples. Rapid immuno-card tests (BINAX NOW Influenza A and B, Inverness Medical, Princeton, NJ) were performed initially on all NPA samples from December - April of 2007-8 and 2008-9. No further testing was performed on positive samples; DFA, shell vial, and tube culture were performed on all samples with a negative immuno-card result.

From May through December 2009, all influenza A positive samples from admitted children were sent to The Maryland Department of Health and Mental Hygiene and confirmed by real-time reverse transcriptase-PCR as novel influenza A (H1N1) as described by the Centers for Disease Control and Prevention (CDC) [12].

Statistical Analysis
Statistical analyses were performed using Stata version 10.0 (STATA Corp., College Station, TX) and the R statistical package (version 2.10.1). Comparisons between patients with seasonal influenza and nH1N1 influenza were performed using Fisher's exact test for non-parametric data and Student's t-test with unequal variances for continuous variables. Hospital LOS was log transformed to achieve a normal distribution and analyzed using linear regression and Poisson regression models. Models including interaction terms and excluding high leverage observations were fitted and residual analysis including residuals plots, Q-Q plots, and added variable plots were examined for violations of regression model assumptions. All variables potentially associated with LOS based on univariable analysis, previous studies, or hypothesized relationships were included in the final linear model to ensure adjustment for their effects. Two-

sided p-values of < 0.05were treated as statistically significant for all tests. The Johns Hopkins University Institutional Review Board approved the study with a waiver of informed consent.

Results

We identified 133 pediatric patients with a laboratory-confirmed diagnosis of seasonal influenza during the 2007-9 seasons. Coincidentally, we identified 133 children with laboratory-confirmed nH1N1 who met our inclusion criteria. The first confirmed nH1N1 virus infection at JHCMSC occurred on May 1st, 2009 and the last case included in this study was diagnosed on November 25th, 2009. Figure 1 depicts the epidemic curve of nH1N1 and seasonal influenza during the prior two epidemic periods at JHCMSC. Similar proportions of children with positive laboratory testing for influenza in the emergency room were admitted to JHCMSC during the nH1N1 pandemic and prior influenza seasons (38% vs. 47%, p = 0.12). There was no difference in the percentage of hospitalized patients admitted directly to the PICU (19% vs. 18%, p = .99).

We aggregated SI data from the two prior seasons because patients in the 2007-8 and 2008-9 seasons were not significantly different in terms of demographic features, underlying medical conditions, clinical course, and outcomes (data not shown). All patients had valid reasons for admission including hypoxia, respiratory distress, shock requiring pressors, immunocompromised and febrile, neonates with fever, or sickle cell disease

with fever. These patient types were equally distributed between the seasons (p ≥ 0.17).
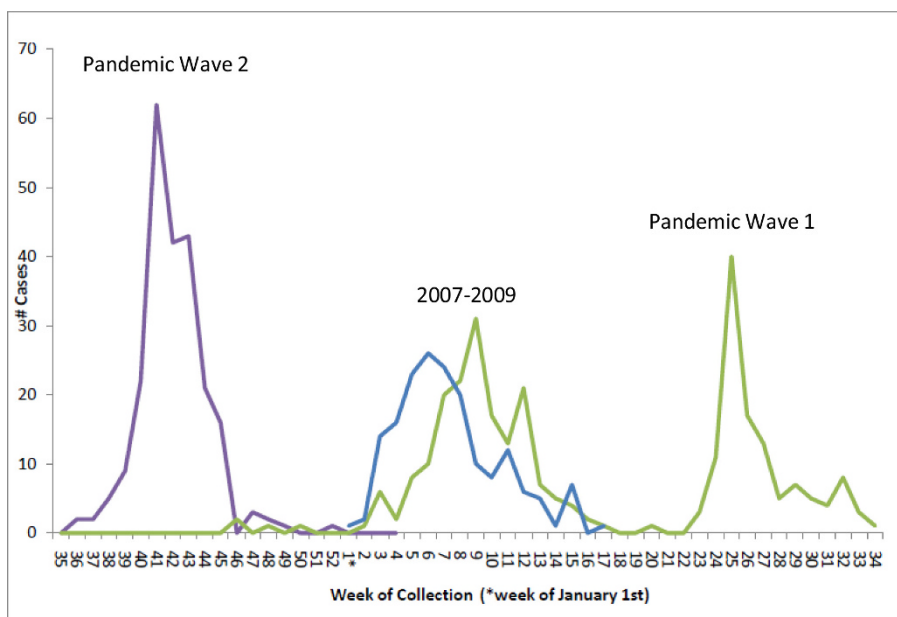
Demographics and presenting symptoms
Children admitted with SI and nH1N1 influenza were similar with regards to age, race, and gender (Table 1). Presenting symptoms were also similar among patients with SI and nH1N1 influenza infection (Table 1); except seizures were reported in 19 (14%) of the children with SI and 5 (4%) of the children with nH1N1 (p = 0.004). Eleven of the children admitted for SI and 4 of the children admitted for nH1N1 who presented with seizures had no known underlying seizure disorder.

Preexisting Medical Conditions
Thirty-five (26%) children admitted with seasonal influenza and 24 (18%) patients with nH1N1 had no preexisting medical conditions (p = 0.14). Twenty (15%) SI and 40 (30%) nH1N1 admissions had an underlying diagnosis of asthma (p < 0.01). Neuromuscular disorders were more prevalent in children admitted with SI compared with nH1N1 (18% vs.7%, p < 0.01). There were otherwise no significant differences with regards to underlying medical conditions between the two groups. (Table 2)

Antimicrobial use
Based on CDC guidelines, and in contrast to SI epidemics, antiviral therapy was recommended for all admitted patients with nH1N1 [5]. Thirty-seven (28%)

Figure 1 Epidemic curve of pandemic influenza A H1N1 and seasonal influenza (2007-2008 and 2008-2009) for children admitted to The Johns Hopkins Children's Medical and Surgical Center.

Table 1 Demographic characteristics, presenting symptoms, and diagnostic testing of children admitted with seasonal influenza (2007-2009) and 2009 novel influenza A (nH1N1) infection

	Seasonal influenza	nH1N1 influenza	p-value
Demographic characteristics	133	133	
Age			
Mean (SD)	7.0 (5.7)	7.3 (5.4)	.64
Median	5.0	6.0	
Race			.43
African American	76 (57%)	83 (62%)	
Asian	2 (2%)	5 (4%)	
Caucasian	47 (35%)	37 (28%)	
Hispanic	8 (6%)	8 (6%)	
Gender			.81
Male	67 (50%)	70 (53%)	
Female	66 (50%)	63 (47%)	
Presenting Symptoms[†]			
Upper respiratory tract	110 (83%)	116 (87%)	.39
Lower respiratory tract	55 (41%)	61 (46%)	.50
Gastrointestinal	35 (26%)	43 (32%)	.35
Mylagias	14 (11%)	8 (6%)	27
Headaches	11 (8%)	18 (14%)	.24
Seizures	19 (14%)	5 (4%)	< .01
Lethargy	33 (25%)	40 (30%)	.41
Diagnostic Testing[††]			
Rapid immuno-card[†††]	55 (41.4%)	N/A	
Direct fluorescent antibody	78(33%)	39 (29%)	.39
Shell vial culture	36 (46%)	90 (68%)	.02
Tube culture	16 (21%)	4(3%)	.40

[†] Fever was part of inclusion criteria, [††] By 1st positive test, [†††] If positive for seasonal influenza no further testing performed

Table 2 Preexisting medical conditions among children admitted with seasonal influenza (2007-2009) and novel influenza A H1N1 (nH1N1) infection

	Seasonal influenza	nH1N1 influenza	p-value
None	35 (26%)	24(18%)	.14
Obesity[†]	49 (46%)	51(45%)	1.00
Asthma	20 (15%)	40 (30%)	< .01
Sickle Cell Disease	17 (12.8%)	26 (20%)	.18
Neuromuscular Disorder	24 (18%)	9 (7%)	< .01
Diabetes Mellitus (type 1)	2 (2%)	2 (2%)	1.00
Chronic Lung Disease	15 (11%)	15 (11%)	1.00
Malignancy	13 (10%)	11(8%)	.83
Immunodeficiency[††]	10 (8%)	4 (3%)	.17
Prematurity (24-37 w)	5 (4%)	10 (8%)	.29
Cardiac disorder	8 (6%)	5 (4%)	.57
Metabolic disorder	7 (5%)	7 (5%)	1.00
Renal Failure	3 (2%)	1 (1%)	.62
Cystic Fibrosis	4 (3%)	3 (2%)	1.00

[†] Body mass index ≥90%, [††] HIV, solid organ transplant, immunodeficiency, corticosteroids ≥ 2 mg/kg/day for >14 days

aureus in another 3 children, and *Streptococcus pneumoniae* in 3 children. One child grew *Streptococcus pyogenes* in a blood culture. No bacteremia was identified in any of the children with nH1N1.

Outcomes

The median LOS for SI was 2 days longer than nH1N1; 5 days [IQR 3-7] vs. 3 days [IQR 2-4]. (Table 4) One patient in the SI cohort had a LOS of 254 days due to complications unrelated to influenza; however, mean LOS remained significant after this outlier was removed (p < 0.001). After adjusting for age, race, gender, number of co-morbid illnesses, presence of a neuromuscular disorder, asthma, obesity, presence of an infiltrate concerning for bacterial pneumonia, antiviral therapy, and >48 hours of antibiotic use, children with SI had 1.73 times longer LOS (95% CI 1.35 - 2.13) than children with nH1N1.

Thirty-seven (28%) SI cases and 27 (20%) nH1N1 cases (p = 0.20) were admitted to the PICU. Sixteen (12%) of the SI children required noninvasive positive pressure ventilation compared with 11(8%) of the nH1N1 children (p = 0.31). There was a trend towards more children with SI requiring mechanical ventilation compared with nH1N1 (16 vs.7, respectively p = 0.08). One patient, with no underlying medical conditions, diagnosed with SI required extracorporeal membrane oxygenation. This patient subsequently died. There were no deaths in children admitted with nH1N1.

children with SI and 106 (80%) children admitted with nH1N1 received antiviral therapy with activity against influenza (p < 0.001). When stratifying LOS based on influenza type and antiviral therapy, LOS was not modified. (Table 3) Chest imaging was performed on a significantly higher proportion of children with nH1N1 compared with SI (92% vs. 83%, p = 0.03). However, similar percentages of children in both groups met diagnostic criteria for bacterial pneumonia (23% vs. 23%). Interestingly, 61 (72%) of nH1N1 and 37 (36%) SI children, received treatment courses of antibiotics for a diagnosis of "bacterial pneumonia" (p < 0.01).

Ten children admitted for SI had bacteremia. Blood cultures grew methicillin-resistant *Staphylococcus aureus* in 3 children, methicillin-susceptible *Staphylococcus*

Table 3 The timing of antiviral therapy and length of stay among children admitted with seasonal influenza (2007-2009) and novel H1N1 influenza (nH1N1)

	Seasonal influenza LOS[†]	nH1N1 influenza LOS[†]	p-value
No antiviral therapy	7.2 days (n = 92)	3.6 days (n = 27)	< .01
Antiviral therapy	6.7 days (n = 37)	4.4 days (n = 106)	.03
Antiviral therapy ≥48 hours after symptom onset or no antiviral therapy	7.2 days (n = 120)	4.5 days (n = 82)	< .01
Antiviral therapy ≤48 hours of symptom onset	5.6 days (n = 12)	3.7 days (n = 51)	.11

[†] Median length of stay, (n = number in each sample)

Discussion

It is critical to understand outcomes for infections to ensure appropriate planning and utilization of healthcare resources. We compared the clinical outcomes of nH1N1 to those of SI in a large cohort of hospitalized children. We found that children admitted with epidemic influenza over the past two influenza seasons (2007-9) appeared to have a longer adjusted LOS, with a median of almost 2 more days of hospitalization than children admitted for nH1N1. Median LOS in our population of children was somewhat higher than reported in other retrospective cohort studies and may be related to the higher percentage of children with high-risk medical conditions in our cohort compared with other studies [10,13].

Despite initial concerns about severity of disease expected for pandemic nH1N1, our data demonstrates that outcomes among patients with SI are at least as concerning. This is particularly relevant as there was a concerted effort to improve infection prevention and control practices, immunization use, and bed allotment for the anticipated large numbers of critically ill children with nH1N1[1-6]. Based on results from our study,

some of these practices may need to be sustained on an annual basis for SI.

The significance of SI appears to be underappreciated by the general population and the health care community. Although the majority of epidemic influenza virus infection is usually mild, influenza has the potential to cause severe disease, particularly in young children and children with underlying medical conditions [14,15]. Children are disproportionately affected by hospitalization rates during SI epidemics. A review of a national database found that the relative risk (RR) for an influenza-associated hospitalization relative to death was estimated to be 270 for children 5 years of age and under, compared to 11 amongst adults aged 50-64 [8]. While mortality is often used to estimate the effect of influenza among adults, it may be an insensitive indicator of the effect of influenza in children as the primarily burden is related to its morbidity [16,17].

Among healthy-children, oseltamivir has been shown to reduce median duration of influenza illness by 36 hours [18]. Although the decreased LOS with nH1N1 could be attributed to wider antiviral use in this population, our data does not support this interpretation. After

Table 4 Non-pharmacologic treatments and outcomes of children admitted with seasonal influenza (2007-2009) and novel influenza A H1N1 (nH1N1)

		Seasonal influenza	nH1N1 influenza	p-value
Length of Stay				0.02
	Mean (SD)	8.9 (23.0) days	4.2 (4.8) days	
	Median (Range)	5 (1 - 254)	3 (1 -32)	
PICU admission		37 (28%)	27 (20%)	0.20
Need for noninvasive positive pressure ventilation		16 (12%)	11 (8%)	0.31
Need for mechanical ventilation		16 (12%)	7 (5%)	0.08
Days of oxygen				0.14
	Mean (SD)	8.7 (19.3)	4.2 (5.3)	
	Median (Range)	4 (1 -140)	2.5 (1-30)	
Days of positive pressure ventilation or mechanical ventilation				0.74
	Mean (SD)	7.04 (1.71)	6.14(1.87)	
	Median (Range)	5(1-38)	2.5 (1-24)	
PICU length of stay				0.20
	Mean (SD)	10.9 (29.3) days	4.5 (5.7) days	
	Median (Range)	4 (1- 179)	2 (1 - 26)	

stratifying by antiviral therapy and influenza type, the difference in LOS between SI and nH1N1 pediatric admissions persisted and antiviral therapy did not appear to significantly influence LOS in our study. Prospective data are needed to define the relative benefits of early antiviral therapy in hospitalized pediatric patients.

In both SI and nH1N1 patients in our cohort, antibiotics were prescribed for bacterial pneumonia when criteria for this diagnosis were not fulfilled. Almost 50% of patients with nH1N1 who received antibiotics for a diagnosis of "bacterial pneumonia" did not meet clinical criteria. Unnecessary prescription of antibiotics may have been related to the general apprehension in the health care community with regards to pandemic nH1N1. Antibiotics have the potential for associated toxicities, costs, and the development of multi-drug resistant organisms. Future studies are needed to better determine the criteria for antibiotics for influenza-related bacterial complications.

During the nH1N1 pandemic, there were widespread media efforts to educate the public about potential consequences of influenza and need for vaccination, especially for the most high-risk groups. Given that annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications, additional efforts need to be made to ensure annual SI vaccination of all children, particularly children at higher risk for influenza complications [8,9,14,15,19-22]. Our results emphasize the need for vaccination against seasonal influenza in order to reduce its associated morbidity.

There are several limitations of our study. First, because of the heightened awareness associated with nH1N1, there is the possibility that the influence of pandemic influenza publicity may have lowered the threshold for admission of nH1N1 cases when compared with SI cases. In our review, all children admitted to the hospital had valid reasons for hospital admission and these reasons were distributed equally between patients with nH1N1 and SI. As other measures to determine if the threshold for hospitalization differed during the pandemic period as compared to the prior two influenza seasons, we assessed the proportion of hospitalized patients directly admitted to the PICU and the proportion of children with laboratory-confirmed influenza-like illness observed in the emergency room admitted to the hospital. There was no difference in these proportions further suggesting that these admissions were likely justified. The proportion of children evaluated in the emergency room and subsequently admitted to the hospital in our cohort is comparable to what has been previously reported in the literature for SI [10].

Second, no conclusions can be made regarding the differences in the virulence of the strains of influenza virus from this paper as we were unable to compare strain types. Children admitted with SI in the 2007-8 and 2008-9 seasons were not significantly different in terms of demographic features, underlying medical conditions, clinical course, and outcomes; however, we recognize that influenza types and subtypes, which vary from season to season, have differential effects on morbidity and mortality [23-25]. Our results demonstrate that SI 2007-9 was at least as significant a cause of pediatric morbidity as nH1N1.

Conclusions

Pandemic nH1N1 received considerable attention with strong media messages urging people to be vaccinated and encouraging improved infection control efforts. As our study strengthens the growing body of evidence demonstrating that SI results in significant morbidity in the pediatric population, we believe that the emphasis on influenza vaccination should be continued on an annual basis and not solely reserved for influenza pandemics.

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