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Advanced age and asthma are associated with severe disease in children with pandemic H1N1 influenza; a retrospective cross sectional study of risk factors for severe pandemic H1N1 influenza in children

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A retrospective cross sectional study of children admitted to hospital with pandemic H1N1 influenza; advanced age and asthma are associated with severe disease compared to seasonal influenza

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ABSTRACT

Objective: Limited data exist on clinical outcomes and risk factors for severe disease from pandemic H1N1 influenza (pH1N1) versus seasonal influenza in children. This study's objective was to compare risk factors (including age and underlying asthma) for admission to hospital and the intensive care unit (ICU) in children with pH1N1versus those with seasonal influenza. Secondary goals included comparison of demographic characteristics, clinical features, other markers of illness severity, and effect of antiviral therapy and diagnostic methods on outcomes in children with pH1N1 versus seasonal influenza.

Design: Retrospective analysis of children admitted to a pediatric referral hospital with pH1N1 (n=176) versus seasonal influenza A (n=200).

Results: Children admitted with pH1N1 were older than seasonal influenza A admissions (hospital admission: 6.5 vs 3.3 years; ICU admission: 7.3 vs 3.6 years). Children hospitalized pH1N1 were more likely to have a pre-existing diagnosis of asthma (15% vs 5%); however there was no difference in the severity of pre-existing asthma between the two groups. After controlling for obesity, asthma (OR 4.59, 95% CI 1.42-14.81) and age > 5 years (OR 2.87, 95% CI 1.60-5.16) were more common as risk factors in admitted children with pH1N1. Asthma was a significant predictor of the need for intensive care in pH1N1 (OR 4.56, 95% CI 1.16-17.89) but not seasonal influenza A patients.

Conclusion: While most pH1N1 cases presented with classic influenza-like symptoms, risk factors for severe pH1N1 disease differed from seasonal influenza A. Older age and asthma were associated with increased admission to hospital and ICU for children with pH1N1.

ARTICLE SUMMARY

Article focus

- Young age and underlying medical conditions have traditionally been considered risk factors for severe influenza in children.
- Children admitted with H1N1 influenza are more likely to have asthma, however, the impact of asthma severity is unknown.

Key messages

- The presence of asthma and increased age, but not severity of asthma, were more common as risk factors for hospitalization with severe H1N1 influenza than with seasonal influenza A.
- These results suggest that in future pandemics, certain high-risk groups may be more adversely affected than expected with seasonal influenza.
- Treatment of H1N1 influenza with oseltamivir did not appear to be associated with differing outcomes or severity of disease.

Strengths and limitations of this study

- The strength of this study is that it compares a large number of children admitted with microbiologically confirmed pH1N1 to those admitted over five years with seasonal influenza A. For each admitted child with suspected asthma, at least two physicians reviewed the case to confirm a diagnosis of pre-existing asthma and to grade the asthma as mild, moderate, or severe.

- The main limitations to this study include its retrospective design, single-center site, the inability to calculate population-based rates, and that the number of admitted patients with asthma, particularly to ICU, was small.

INTRODUCTION

Infants and young children have traditionally been considered at risk for severe seasonal influenza A.[1-2] It is not known if pandemic H1N1 influenza (pH1N1) has differing risk factors or clinical characteristics compared to seasonal influenza A. Recently published pediatric studies suggest that while most cases of pH1N1 are relatively mild, older children, especially those suffering from asthma and obesity, may be at higher risk for severe disease. Rates of pediatric intensive care admission, mechanical ventilation, and mortality associated with pH1N1 may be higher than those associated with seasonal influenza.[3-5]

A previous study from our center following the first wave of the pandemic found that children admitted with pH1N1 were significantly older and more likely to have asthma than those admitted with seasonal influenza A.[6] In late 2009, a second wave of pH1N1 resulted in more admissions to our hospital. The increase in pH1N1 cases allowed us to verify the findings of our initial study, and identify independent risk factors for admission to the intensive care unit (ICU) among pH1N1 and seasonal influenza hospitalized cases through multivariable analyses. Finally, we wanted to understand how differences in diagnostic methods and treatment between pH1N1 and seasonal influenza might affect outcomes. Thus our primary goals in this study were to compare the age-adjusted proportions of asthmatics among children admitted to hospital and the ICU with pH1N1 relative to those admitted with seasonal influenza, and determine whether age and asthma are independent predictors of ICU admission in pH1N1 as well as seasonal influenza infection. Secondary goals were to describe clinical features, other markers of

illness severity, and effect of antiviral therapy and diagnostic methods on outcomes in children with pH1N1.

DESIGN

We identified and reviewed health records of all laboratory-confirmed cases of pH1N1 admitted in 2009 to The Hospital for Sick Children (SickKids), a large pediatric referral hospital in Toronto, Canada with over 14,000 admissions per year.[7] We compared children admitted with pH1N1 to those admitted with seasonal influenza A during the 2004-2005 through 2008-2009 influenza seasons. In order to exclude potential hospital-acquired infections, only children who developed influenza-like symptoms prior to the third day of admission were included in this study. All patients with influenza-like illness were initially screened for influenza by direct immunofluorescence assay (DFA). During the first wave of the pandemic, all inpatient respiratory samples were tested using reverse transcription polymerase chain reaction (RT-PCR) with primers developed by the National Microbiology Laboratory, Winnipeg, Manitoba.[8] During the second wave, all inpatient respiratory samples were tested with a commercial real-time RT-PCR kit (RT-PCR Kit 1.0, Astra Diagnostics, Hamburg). Seasonal influenza cases were identified through DFA and/or viral culture. Two physicians (MB and DT) reviewed each potential case of asthma to confirm the diagnosis and determine severity (Web Table). Any discrepancies were adjudicated by an asthma specialist (PS).

Comparisons were made between the pH1N1 and seasonal influenza A groups and between the first and second waves of pH1N1. Differences in normally distributed continuous variables were analyzed using Student's *t* test. Comparisons of skewed data

(length of stay and age) were analyzed using non parametric Mann-Whitney and Kruskal-Wallis methods. The chi^2 or Fisher's exact test was used to compare categorical variables between groups and as a test of heterogeneity among multiple proportions. We performed multivariable logistic regression to 1) adjust for the potential confounding effect of age (as a continuous variable and categorical variable) on asthma as a risk factor in comparing the severity of pH1N1 and seasonal influenza; and 2) construct models of risk for ICU admission in pH1N1 and seasonal influenza A infection that included age (as a continuous variable and categorical variable), asthma, and obesity as independent variables. All statistical analysis was performed using Stata SE 10.[9]

SM and DT conceived of and designed the study, conducted the anlaysis, interpreted the data, and drafted the original manuscript. PP, MB, PS, SO, MB and UA contributed to the analysis and interpretation of data. All authors critically revised the article for important intellectual content and gave final approval of the version to be published. The SickKids Research Ethics Board approved and waived individual informed consent for this study.

RESULTS

179 children with pH1N1 were admitted in 2009 in two waves (May to July 2009 n=58, September to December 2009 n=118) (Figure 1), of whom 3 were excluded because the onset of symptoms was more than three days after admission. 200 children were admitted to hospital with seasonal influenza A over five seasons (2004-2005 n=46; 2005-2006 n=26; 2006-2007 n=36; 2007-2008 n=56; 2008-2009 n=36). There were no

differences across the years of seasonal influenza cases in terms of demographic characteristics, underlying risk factors, or outcomes (data not shown).

Demographic Characteristics

Characteristics of children with pH1N1 and seasonal influenza are shown in Table 1. Children with pH1N1 were significantly older than those with seasonal influenza A (6.5 vs 3.3 years, p-value <0.01). The proportion of children over 5 years was higher in pH1N1 (61% vs 38%, p<0.01) whereas the proportion under 2 years was higher in seasonal influenza A (37% vs 18%, p<0.01). Children admitted to ICU with pH1N1 were older than those with seasonal influenza A (7.3 vs 3.6 years, p=0.02).

Disease Severity

Requirement and duration of oxygen therapy, ICU admission, mechanical ventilation and total length of hospital stay are shown in Table 1. 59 (34%) patients admitted with pH1N1 required oxygen supplementation. 32 (18%) children with pH1N1 required admission to ICU and of these, 18 (56%) required mechanical ventilation. There was no difference in ICU admission or need for mechanical ventilation between pH1N1 and seasonal influenza A. More children admitted during the first wave required oxygen than those admitted during the second wave (47% vs 28%, p=0.01). When examining only children who did not receive antiviral therapy, the difference in oxygen use between

waves 1 and 2 remained significant (48% vs 19%, p=0.03). None of the pH1N1 patients died.

Clinical and Laboratory Characteristics

Most pH1N1 cases presented with fever and cough. More than one-third had gastrointestinal symptoms (Table 2). The laboratory results of children admitted with pH1N1 are shown in Table 3. Four patients had positive blood cultures during their admission (*Streptococcus pneumoniae* (2), Viridans group *Streptococcus* (1), *Pseudomonas aerugenosa* (1)).

Risk Factors

Children with pH1N1 compared to those with seasonal influenza were more likely to have history of asthma (15% vs 5%, p<0.01); however, there was no difference in the severity of asthma between the two groups (Table 4). Cardiac disease (11% vs 4%, p=0.02) and age under 2 years with no other risk factors (18% vs 9%, p=0.02) were more common in children hospitalized with seasonal influenza. In patients requiring intensive care, history of asthma was more common in pH1N1 than in seasonal influenza A; however, this difference did not reach statistical significance (19% vs 3%, p=0.10).

In a multivariable analysis including obesity, age category, and asthma, both age greater than 5 (with age <=2 as reference) (OR 2.87 95% CI 1.60-5.16) and history of asthma (OR 4.59, 95% CI 1.42-14.81) were more common as risk factors in admitted children with pH1N1 compared to seasonal influenza A. In the same analysis but using age as a continuous rather than categorical variable, asthma remained more common as a

risk factor in pH1N1 (OR 8.77, 95% CI 1.85-41.52). Table 5 displays multivariable logistic regression analyses for predictors of ICU admission with pH1N1 and with seasonal influenza A infection. In multivariable models including obesity, age category and underlying asthma as independent variables, asthma was a significant predictor of the need for intensive care with pH1N1 infection (OR 4.56, 95% CI 1.16-17.89) but not with seasonal influenza A infection. When the multivariable models included age as a continuous instead of categorical variable, underlying asthma remained a significant predictor of the need for ICU care with pH1N1 infection (OR 5.22, 95% CI 1.23-22.08).

In children with asthma, 29% of those with pH1N1 versus 33% of those with seasonal influenza presented with acute wheeze (p=0.81). In children without underlying asthma, there was no difference in presentation with acute wheeze in those with pH1N1 (15%) and those with seasonal influenza (12%), p=0.51.

Diagnosis and Management

At our institution, seasonal influenza was diagnosed by DFA supplemented with viral culture whereas cases positive by DFA for pH1N1 required confirmation by PCR. To assess the potential impact of differing diagnostic methods, we re-analyzed all cases restricting solely to those positive by DFA. The only changes from the previously presented results were that the length of stay in hospital was longer in seasonal influenza (median 3.5 vs 3 days, p=0.03) and that underlying chronic lung disease (excluding asthma) was no longer significantly more common in those admitted to ICU with seasonal influenza A (p=0.09).

Children with pH1N1 were more likely to receive antiviral therapy (61% vs 8%, p<0.01). There were significant changes in how pH1N1 was managed between waves; 19% of children received antiviral therapy during wave 1 compared to 82% in wave 2 (p < 0.01). However, when comparing all children with pH1N1 who received antiviral therapy to those who did not, there were no significant differences in the need for ICU admission (22% vs 14%, p=0.07), mechanical ventilation (14% vs 8%, p=0.08), or length of stay in hospital (median duration 3 days vs 3 days, p=0.68). To test if sicker children received antiviral therapy, we compared all available Canadian Triage and Acuity Scores[10] (CTAS), a standardized measure of disease acuity, between pH1N1 patients who did (n=65), and did not (n=42) receive antiviral therapy and did not find a significant difference between the two groups (p=0.70).

DISCUSSION

Most cases of pH1N1 presented with a classic influenza-like illness, with no convincing evidence that pH1N1 was more severe than seasonal influenza. However, the risk factors for admission to hospital and ICU differed between pH1N1 and seasonal influenza. Older age was a greater risk factor for admission to hospital and ICU for pH1N1 and asthma was a greater risk factor for hospitalization for pH1N1. These results corroborate earlier research based on fewer cases from our institution[6] as well as a recent study from Colorado comparing children admitted to hospital with pH1N1 to those with 2008-09 seasonal influenza A or B.[11] Conversely, underlying cardiac disease in those admitted to hospital and non-asthma chronic lung disease in those admitted to ICU were significantly more common in seasonal influenza. These results suggest that risk

factors for new influenza strains and that high-risk groups during future pandemics may not be simply extrapolated from the experience with seasonal strains.

Guidelines from the Public Health Agency of Canada highlighted children less than 2 years of age as a high-risk group for pH1N1.[12] However, our results of a median age of 6.5 years in hospitalized pH1N1 patients is remarkably similar to studies from California[13] (median age 6 years) and Japan[14] (median age 7 years). While we found the proportion of hospitalized cases higher in older age categories in pH1N1, in the absence of community population-based epidemiologic data, we are not able to comment on any differences that may exist in age-specific attack, hospitalization, or ICU admission rates in our study population.

This study was not designed to identify the impact of differing management strategies on severity and outcomes of pH1N1. However, in contrast to the first study from our centre, in this study, differences in antiviral use between waves allowed for an interesting natural experiment. Overall, during the first wave, 0%, 46%, and 14% of children aged under 2 years, 2 to 4 years, and 5 years and over respectively received oseltamivir. During the second wave, 65%, 88%, and 86% of children under 2 years, 2 to 4 years, and 5 years and over respectively received antiviral therapy. While there was no difference in markers of disease severity including ICU admission, mechanical ventilation, and length of hospital stay between the two pandemic waves, there was a greater need for oxygen in children hospitalized during wave 1. This difference only remained significant when restricting the analysis to those who did not receive antiviral therapy. This finding may reflect increased antiviral use directed at sicker children during wave 2, while the mildest cases did not receive antivirals.

In the previous analysis of the first wave of pH1N1 in Toronto, asthma was a more significant risk factor for pH1N1 than for seasonal influenza.[6] In this study, with more than 3 times the number of pH1N1 cases, we confirm the significance of asthma as a major risk factor; controlling for obesity and age (as a continuous variable) asthma was more likely to be present in hospitalized children with pH1N1 (OR 4.59, 95% CI 1.42-14.81 than with seasonal influenza A. In pH1N1 cases, asthma was associated with admission to ICU (OR 4.56, 95% CI 1.16-17.89). This is in contrast to seasonal influenza A in which underlying asthma was not significantly associated with ICU admission (OR 2.47, 95% CI 0.24-25.80). We did not find that the severity of asthma was differentially associated with hospitalization or ICU admission between pH1N1 and seasonal influenza. While 6 (19%) ICU admissions with pH1N1 had asthma (4 mild, 1 moderate, and 1 severe) compared to only 1 (3%) (mild) ICU admission with seasonal influenza, the numbers were too small to be able to demonstrate a difference. In a large California study of 345 children hospitalized or who died with pH1N1, 31% of hospitalized children and 34% of ICU and/or fatal cases had asthma.[13] In Japan, 14% of non-severe cases of pH1N1 and 47% of severe cases had asthma,[14] while a United Kingdom study found asthma was present in 16% of children <16 years and 31% of adults.[15] None of these studies examined severity of asthma or the differences between pH1N1 and seasonal influenza.

Immunologic studies of severe pH1N1 cases have shown delayed expression of genes involved in the adaptive immune response, delayed viral clearance, and increased levels of innate immunity mediators involved in the Th1 and Th17 response.[16-17] Children with underlying asthma and other groups (such as pregnant women) thought to

be at higher risk for severe pH1N1 disease[18-20] may have an altered immunologic and inflammatory response to this virus resulting in increased disease severity. Interleukin-5 (IL-5) has been shown to be highly expressed in bronchial mucosa of asthmatics,[21] is a key player in eosinophilic inflammation,[22] and has been found to be higher in serum of pH1N1 patients with pneumonia than those without.[23] However, further research is needed to fully understand this association. While there is some evidence in adults that adjuvant corticosteroids in severe pH1N1 may increase mortality,[24] the impact of inhaled corticosteroids in childhood asthma on pH1N1 severity is not known and this study was not designed nor powered to address this question.

Influenza vaccination coverage in asthmatic children has been poor in many countries.[25,26] Some physicians remain skeptical of the need for vaccinating all asthmatic children [27], while others tend to prioritize children with more severe asthma.[28] Definitive data has been elusive [29]. Our findings suggest that physicians should ensure all asthmatic children under their care have been vaccinated against pH1N1 (which is currently included in the standard seasonal influenza vaccine), regardless of severity of asthma, at least until randomized controlled trial data becomes available.

There are several limitations to this study including its retrospective design, single-center site, and inability to calculate population-based rates. The number of admitted patients with asthma, particularly to ICU, was small, and this may have hindered our ability to identify differences in risk based on severity. Additionally, we identified only the single most important underlying risk factor (with the exception of asthma, obesity, and age which were all collected for each patient) and thus, we were unable to explore interactions between risk factors in patients with multiple co-

morbidities. Our metrics of influenza severity–ICU admission and duration of stay–may be impacted by non-medical factors such as bed availability. In regards to oxygen use, we did not have data on oximetry or criteria that were used by physicians to start or stop oxygen supplementation and thus it was difficult to determine the significance of the difference seen in wave 1 versus wave 2. In regards to oseltamivir use, we did not extract data on dosage, duration, or when the medication was begun. However, the use of oseltamivir in this study was at the discretion of the attending physician and thus reflective of 'real life' use.

CONCLUSION

Risk factors for severe disease, specifically the presence of underlying asthma and increased age, differed between pH1N1 and seasonal influenza in children. There was no difference in overall disease severity. These results suggest that in future pandemics with new influenza strains, high-risk groups may be different than those traditionally considered as such. The reasons for the differing influence of asthma and age on host response to pH1N1 are not understood and further study of the underlying mechanisms contributing to these differences may shed new light on the host-pathogen immunobiology of a pandemic strain of influenza virus. This study emphasizes the need to ensure that all asthmatic children have been vaccinated against pH1N1 influenza, regardless of the severity of their asthma.

	pH1N1 Wave 1 versus Wave 2			pH1N1 versus Seasonal Influenza A		
Characteristic	1st Wave (n=58)	2nd Wave (n=118)	p value	pH1N1 (n=176)	Seasonal (n=200)	p value
Sex, male, no. (%)	35 (60)	72 (61)	0.93	107 (61)	108 (54)	0.18
Age, yr, median (IQR)	6.4 (3.4-10.1)	6.5 (2.9-11.4)	0.81	**6.5 (3.0-10.6)**	**3.3 (1.4-7.8)**	**<0.01**
Age group, yr, no (%)						
<2	8 (14)	23 (19)	0.35	**31(18)**	**74(37)**	**<0.01**
2 to 5	13 (22)	24 (20)	0.75	37(21)	54(27)	0.18
>5	37 (64)	71 (60)	0.64	**108(61)**	**72(36)**	**<0.01**
Admitted to ICU						
No. (%) of children	12 (21)	20 (17)	0.36	32 (18)	31 (15)	0.49
Age, yr, median (IQR)	5.8 (3.2-7.3)	9.2 (5.4-11.4)	0.13	**7.3 (4.0-10.6)**	**3.6 (1.5-9.7)**	**0.02**
Required Mechanical Ventilation						
No. (%) of children	7 (12)	11 (9)	0.57	18 (10)	19 (10)	0.81
No. (%) of children admitted to ICU	7 (58)	11 (55)	0.85	18 (56)	19 (61)	0.69
Required Supplemental Oxygen						
No. (%) of children	26 (47)	33 (28)	0.01	59 (34)		
Duration of Oxygen, d, median (IQR)	4 (2-6)	3(2-7)	0.73	3 (2-6)		
Length of stay, d, median (IQR)						
In hospital	4 (2-6)	3 (2-5)	0.06	3 (2-5)	4 (2-7)	0.12
In ICU	3.5 (2.5-17)	2 (1.5-5)	0.08	3 (2-8)	2 (1-5)	0.24
Antiviral therapy No. (%)	**11 (19)**	**97 (82)**	**<0.01**	**108 (61)**	**16 (8)**	**<0.01**

Table 1: Demographic and Clinical Characteristics of Pandemic H1N1 and Seasonal Influenza A

Clinical Presentation	Number (%)			
	0 to <2 yrs	2 to <5 yrs	>5 yrs	0 to 18 yrs
Fever	31 (100)	36 (97)	99 (92)	166 (94)
Cough	29 (94)	34 (92)	84 (78)	147 (84)
Gastrointestinal	14 (45)	16 (43)	40 (37)	70 (40)
Wheeze	4 (13)	8 (22)	24 (22)	36 (20)
Pneumonia	11 (35)	12 (32)	29 (27)	52 (30)
Apnea	3 (10)	3 (8)	2 (2)	8 (5)
Seizure	2 (7)	5 (14)	2 (2)	9 (5)
Encephalopathy	1 (3)	1 (3)	2 (2)	4 (2)
Myocarditis	0 (0)	1 (3)	1 (1)	2 (1)
Myositis	0 (0)	0 (0)	2 (2)	2 (1)

Table 2: Clinical Symptoms of Pandemic H1N1 by Age Category

Lab Value	Number (%)
White blood cells ≥ 11.0 x 10^9/L	50 (29)
White blood cells < 4.0 x 10^9/L	33 (19)
Absolute neutrophils >6.6 x 10^9/L	59 (35)
Absolute neutrophils <1.5 x 10^9/L	30 (18)
Absolute lymphocytes < 1.8 x 10^9/L	112 (66)

Table 3: Haematologic laboratory values of children admitted with pH1N1

Footnote: 174 children had complete blood count and 170 had differential performed.

Risk Factor	All Children Admitted to Hospital			Children Admitted to ICU		
	pH1N1 n=176	Seasonal n=200	p value	pH1N1 n=32	Seasonal n=31	p value*
Asthma[§]	**26 (15)[#]**	**9 (5)**	**<0.01**	6 (19)	1 (3)	0.10
Mild Asthma	16(62)	7(78)	0.38	4(67)	1(100)	1.00
Moderate Asthma	6(23)	1(11)	0.44	1 (17)	0(0)	1.00
Severe Asthma	4 (15)	1(11)	0.75	1(17)	0(0)	1.00
Chronic Lung Disease	12 (7)	13 (7)	0.92	**0 (0)**	**5 (16)**	**0.02**
Obesity†	8(7)	14(9)	0.64	3 (20)	2 (9)	0.38
Cardiac Disease	**7 (4)**	**21 (11)**	**0.02**	3 (9)	4 (12)	0.71
Hemoglobinopathy	19 (11)	22 (11)	0.95	1 (3)	1 (3)	0.75
Immunodeficiency	32 (18)	42 (21)	0.49	1 (3)	2 (3)	0.61
Neurologic Impairment	21 (12)	26 (13)	0.76	6 (19)	8 (26)	0.56
Age <2 and no other risk factors	**16 (9)**	**35 (18)**	**0.02**	2 (6)	4 (13)	0.43

Table 4^: Risk Factors for Admission to Hospital and Intensive Care Unit, Pandemic H1N1 versus Seasonal Influenza A

Footnotes: # Percentages in parentheses. *Fisher's exact test used when cell size is small. †Obesity was defined according to guidelines from the Centers for Disease Control as a body mass index ≥ 95th percentile for age in children older than 2 years.[30] Obesity could not be calculated for 45(31%) & 68(54%) children > 2 years in the seasonal and pH1N1 groups respectively. ^ Any

differences between the numbers presented in Table 4 and those from O'Riordan et al. [6] are the result of a re-assessment of all pH1N1 and seasonal influenza cases for this study.

	pH1N1	Seasonal Influenza
Risk Factor	OR (95% CI)	OR (95% CI)
Asthma^	4.56 (1.16-17.89)	2.47 (0.24-25.80)
Obesity	4.18 (0.76-22.95)	1.06 (0.20-5.64)
Age 0 to <2 Years	1.00	1.00
Age 2 to < 5 Years	1.70 (0.30-9.48)	1.40 (0.44-4.44)
Age >5 Years	0.89 (0.19-4.07)	0.62 (0.19-1.98)

Table 5: Multivariable Regression of Asthma, Obesity, and Age Category as Risk Factors for ICU Admission with Pandemic H1N1 and Seasonal Influenza A.

Footnote: ^ Asthma was also common as a risk factor (OR 8.77, 95% CI 1.85-41.52) for admission to hospital in pH1N1 compared to seasonal influenza (with age as continuous variable)

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Competing Interests

None of the authors have any competing interests of conflicts to declare.

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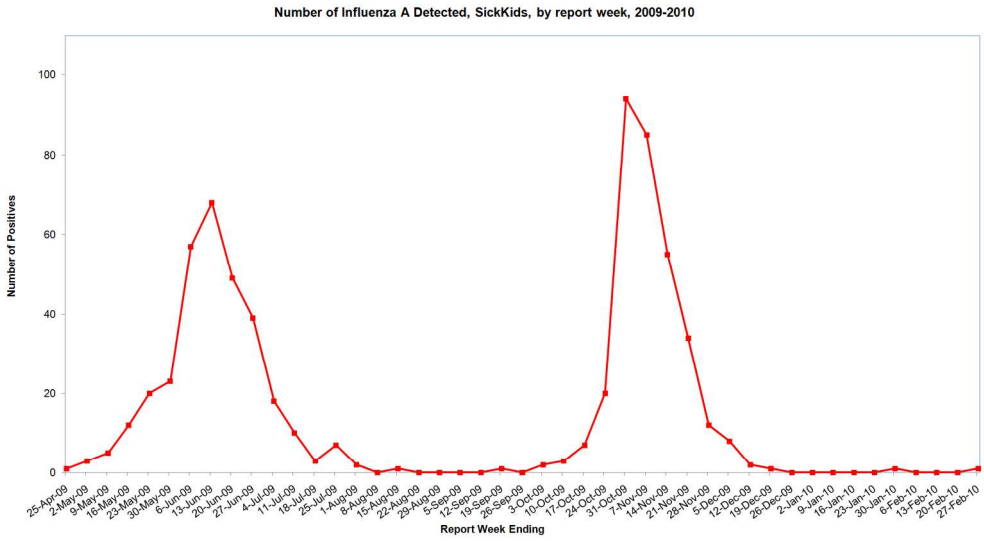

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1**X**	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2**X**	Explain the scientific background and rationale for the investigation being reported
Objectives	3 **X**	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 **X**	Present key elements of study design early in the paper
Setting	5 **X**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 **X**	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7 **X**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* **X**	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 **X**	Describe any efforts to address potential sources of bias
Study size	10 **X**	Explain how the study size was arrived at
Quantitative variables	11 **X**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 **X**	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13* **X**	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* **X**	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15* **X**	Report numbers of outcome events or summary measures
Main results	16 **X**	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 **X**	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18 **X**	Summarise key results with reference to study objectives
Limitations	19 **X**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 **X**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 **X**	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 **X**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A retrospective cross sectional study of risk factors and clinical spectrum of children admitted to hospital with pandemic H1N1 influenza as compared to influenza A

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A retrospective cross sectional study of risk factors and clinical spectrum of children admitted to hospital with pandemic H1N1 influenza as compared to influenza A

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ABSTRACT

Objective: To compare risk factors for severe disease, admission to hospital and intensive care unit (ICU), and other clinical outcomes in children with pandemic H1N1 (pH1N1) versus those with seasonal influenza.

Design: Retrospective analysis of children admitted to hospital with pH1N1 versus seasonal influenza A.

Setting: Canadian tertiary referral children's hospital.

Participants: All laboratory identified cases of pH1N1 in children under the age of 18 years admitted to hospital in 2009 (n=176) and all seasonal influenza A cases admitted to hospital from influenza seasons 2004-05 to 2008-09 (n=200). Children with onset of symptoms more than 3 days after admission were excluded.

Primary and secondary outcome measures: Primary outcomes include admission to hospital and intensive care, need for mechanical ventilation. Secondary outcomes include length of stay in hospital and duration of supplemental oxygen requirement.

Results: Children admitted with pH1N1 were older than seasonal influenza A admissions (hospital admission: 6.5 vs 3.3 years, p<0.01; ICU admission: 7.3 vs 3.6 years, p=0.02). Children hospitalized with pH1N1 were more likely to have a pre-existing diagnosis of asthma (15% vs 5%, p<0.01); however there was no difference in the severity of pre-existing asthma between the two groups. After controlling for obesity, asthma (OR 4.59, 95% CI 1.42-14.81) and age > 5 years (OR 2.87, 95% CI 1.60-5.16) were more common as risk factors in admitted children with pH1N1. Asthma was a significant predictor of the need for intensive care in pH1N1 (OR 4.56, 95% CI 1.16-17.89) but not seasonal influenza A patients.

Conclusion: While most pH1N1 cases presented with classic influenza-like symptoms, risk factors for severe pH1N1 disease differed from seasonal influenza A. Older age and asthma were associated with increased admission to hospital and ICU for children with pH1N1.

ARTICLE SUMMARY

Article focus

- Young age and underlying medical conditions have traditionally been considered risk factors for severe influenza in children.

- Children admitted with H1N1 influenza are more likely to have asthma, however, the impact of asthma severity is unknown.

Key messages

- The presence of asthma and increased age, but not severity of asthma, were more common as risk factors for hospitalization with severe H1N1 influenza than with seasonal influenza A.

- These results suggest that in future pandemics, certain high-risk groups may be more adversely affected than expected with seasonal influenza.

- Treatment of H1N1 influenza with oseltamivir did not appear to be associated with differing outcomes or severity of disease.

Strengths and limitations of this study

- The strength of this study is that it compares a large number of children admitted with microbiologically confirmed pH1N1 to those admitted over five years with seasonal influenza A. For each admitted child with suspected asthma, at least two physicians reviewed the case to confirm a diagnosis of pre-existing asthma and to grade the asthma as mild, moderate, or severe.

- The main limitations to this study include its retrospective design, single-center site, the inability to calculate population-based rates, and that the number of admitted patients with asthma, particularly to ICU, was small.

INTRODUCTION

In a large global pooled analysis of patients of all ages, the risk factors for severe pandemic H1N1 (pH1N1) disease have been found to have some notable differences from seasonal influenza including younger age, obesity, and pregnancy.[1] In the pediatric population, infants and young children have traditionally been considered at risk for severe seasonal influenza A.[2-3] However, recently published pediatric studies suggest that while most cases of pH1N1 are relatively mild, older children, especially those suffering from asthma and obesity, may be at higher risk for severe disease. Rates of pediatric intensive care admission, mechanical ventilation, and mortality associated with pH1N1 may be higher than those associated with seasonal influenza.[4-7]

A previous study from our center following the first wave of the pandemic found that children admitted with pH1N1 were significantly older and more likely to have asthma than those admitted with seasonal influenza A.[8] In late 2009, a second wave of pH1N1 resulted in more admissions to our hospital. The increase in pH1N1 cases allowed us to verify the findings of our initial study, and identify independent risk factors for admission to the intensive care unit (ICU) among pH1N1 and seasonal influenza hospitalized cases through multivariable analyses. Finally, we wanted to understand how differences in diagnostic methods and treatment between pH1N1 and seasonal influenza might affect outcomes. Thus our primary goals in this study were to compare the ageadjusted proportions of asthmatics among children admitted to hospital and the ICU with pH1N1 relative to those admitted with seasonal influenza, and determine whether age and asthma are independent predictors of ICU admission in pH1N1 as well as

seasonal influenza infection. Secondary goals were to describe clinical features, other markers of illness severity, and effect of antiviral therapy and diagnostic methods on outcomes in children with pH1N1.

DESIGN

We identified and reviewed health records of all laboratory-confirmed cases of pH1N1 in children under the age of 18 years admitted in 2009 to The Hospital for Sick Children (SickKids), a large pediatric referral hospital in Toronto, Canada with over 14,000 admissions per year.[9] Cases were identified through a review of microbiology labortatory records. We compared children admitted with pH1N1 to those admitted with seasonal influenza A during the 2004-2005 through 2008-2009 influenza seasons. In order to exclude potential hospital-acquired infections, we excluded any children who developed influenza-like symptoms on or after the third day of admission. Testing was done at the clinical discretion of the attending physician. All patients with influenza-like illness were initially screened for influenza by direct immunofluorescence assay (DFA). During the first wave of the pandemic, all inpatient respiratory samples were tested using reverse transcription polymerase chain reaction (RT-PCR) with primers developed by the National Microbiology Laboratory, Winnipeg, Manitoba.[10] During the second wave, all inpatient respiratory samples were tested with a commercial real-time RT-PCR kit (RTPCR Kit 1.0, Astra Diagnostics, Hamburg). Seasonal influenza cases were identified through DFA and/or viral culture. Two physicians (MB and DT) reviewed each potential case of asthma to confirm the diagnosis and determine severity (Web Table). Any discrepancies were adjudicated by an asthma specialist (PS).

Comparisons were made between the pH1N1 and seasonal influenza A groups and between the first and second waves of pH1N1. Differences in normally distributed continuous variables were analyzed using Student's *t* test. Comparisons of skewed data (length of stay and age) were analyzed using non parametric Mann-Whitney and Kruskal-Wallis methods. The chi-square or Fisher's exact test was used to compare categorical variables between groups and as a test of heterogeneity among multiple proportions. We performed multivariable logistic regression to 1) adjust for the potential confounding effect of age (as a continuous variable and categorical variable) on asthma as a risk factor in comparing the severity of pH1N1 and seasonal influenza; and 2) construct models of risk for ICU admission in pH1N1 and seasonal influenza A infection that included age (as a continuous variable and categorical variable), asthma, and obesity as independent variables. All statistical analysis was performed using Stata SE 10.[11]

SM and DT conceived of and designed the study, conducted the anlaysis, interpreted the data, and drafted the original manuscript. PP, MB, PS, SO, MB and UA contributed to the analysis and interpretation of data. All authors critically revised the article for important intellectual content and gave final approval of the version to be published. The SickKids Research Ethics Board approved and waived individual informed consent for this study.

RESULTS

179 children with pH1N1 were admitted in 2009 in two waves (May to July 2009 n=58, September to December 2009 n=118) (Figure 1), of whom 3 were excluded because the onset of symptoms was more than three days after admission. 200 children were admitted to hospital with seasonal influenza A over five seasons (2004-2005 n=46; 2005-2006 n=26; 2006-2007 n=36; 2007-2008 n=56; 2008-2009 n=36). There were no differences across the years of seasonal influenza cases in terms of demographic characteristics, underlying risk factors, or outcomes (data not shown).

Demographic Characteristics

Characteristics of children with pH1N1 and seasonal influenza are shown in Table 1. Children with pH1N1 were significantly older than those with seasonal influenza A (6.5 vs 3.3 years, p<0.01). The proportion of children over 5 years was higher in pH1N1 (61% vs 38%, p<0.01) whereas the proportion under 2 years was higher in seasonal influenza A (37% vs 18%, p<0.01). Children admitted to ICU with pH1N1 were older than those with seasonal influenza A (7.3 vs 3.6 years, p=0.02).

Disease Severity

Requirement and duration of oxygen therapy, ICU admission, mechanical ventilation and total length of hospital stay are shown in Table 1. 59 (34%) patients admitted with pH1N1 required oxygen supplementation. 32 (18%) children with pH1N1 required admission to ICU and of these, 18 (56%) required mechanical ventilation. There was no difference in ICU admission or need for mechanical ventilation between pH1N1

and seasonal influenza A. More children admitted during the first wave required oxygen than those admitted during the second wave (47% vs 28%, p=0.01). When examining only children who did not receive antiviral therapy, the difference in oxygen use between waves 1 and 2 remained significant (48% vs 19%, p=0.03). None of the pH1N1 patients died.

Clinical and Laboratory Characteristics

Most pH1N1 cases presented with fever and cough. More than one-third had gastrointestinal symptoms (Table 2). The laboratory results of children admitted with pH1N1 are shown in Table 3. Four patients had positive blood cultures during their admission (*Streptococcus pneumoniae* (2), Viridans group *Streptococcus* (1), *Pseudomonas aerugenosa* (1)).

Risk Factors

Children with pH1N1 compared to those with seasonal influenza were more likely to have history of asthma (15% vs 5%, p<0.01); however, there was no difference in the severity of asthma between the two groups (Table 4). Cardiac disease (11% vs 4%, p=0.02) and age under 2 years with no other risk factors (18% vs 9%, p=0.02) were more common in children hospitalized with seasonal influenza. In patients requiring intensive care, history of asthma was more common in pH1N1 than in seasonal influenza A; however, this difference did not reach statistical significance (19% vs 3%, p=0.10). In a multivariable analysis including obesity, age category, and asthma, both age greater than 5 (with age <=2 as reference) (OR 2.87 95% CI 1.60-5.16) and history of

asthma (OR 4.59, 95% CI 1.42-14.81) were more common as risk factors in admitted children with pH1N1 compared to seasonal influenza A. In the same analysis but using age as a continuous rather than categorical variable, asthma remained more common as a risk factor in pH1N1 (OR 8.77, 95% CI 1.85-41.52). Table 5 displays multivariable logistic regression analyses for predictors of ICU admission with pH1N1 and with seasonal influenza A infection. In multivariable models including obesity, age category and underlying asthma as independent variables, asthma was a significant predictor of the need for intensive care with pH1N1 infection (OR 4.56, 95% CI 1.16-17.89) but not with seasonal influenza A infection. When the multivariable models included age as a continuous instead of categorical variable, underlying asthma remained a significant predictor of the need for ICU care with pH1N1 infection (OR 5.22, 95% CI 1.23-22.08). In children with asthma, 29% of those with pH1N1 versus 33% of those with seasonal influenza presented with acute wheeze (p=0.81). In children without underlying asthma, there was no difference in presentation with acute wheeze in those with pH1N1 (15%) and those with seasonal influenza (12%), p=0.51.

Diagnosis and Management

At our institution, seasonal influenza was diagnosed by DFA supplemented with viral culture whereas cases positive by DFA for pH1N1 required confirmation by PCR. To assess the potential impact of differing diagnostic methods, we re-analyzed all cases restricting solely to those positive by DFA. The only changes from the previously presented results were that the length of stay in hospital was longer in seasonal influenza (median 3.5 vs 3 days, p=0.03) and that underlying chronic lung disease (excluding

asthma) was no longer significantly more common in those admitted to ICU with seasonal influenza A (p=0.09).

Children with pH1N1 were more likely to receive antiviral therapy (61% vs 8%, p<0.01). There were significant changes in how pH1N1 was managed between waves; 19% of children received antiviral therapy during wave 1 compared to 82% in wave 2 (p < 0.01). However, when comparing all children with pH1N1 who received antiviral therapy to those who did not, there were no significant differences in the need for ICU admission (22% vs 14%, p=0.07), mechanical ventilation (14% vs 8%, p=0.08), or length of stay in hospital (median duration 3 days vs 3 days, p=0.68). To test if sicker children received antiviral therapy, we compared all available Canadian Triage and Acuity Scores[12] (CTAS), a standardized measure of disease acuity, between pH1N1 patients who did (n=65), and did not (n=42) receive antiviral therapy and did not find a significant difference between the two groups (p=0.70).

DISCUSSION

Most cases of pH1N1 presented with a classic influenza-like illness, with no convincing evidence that pH1N1 was more severe than seasonal influenza. However, the risk factors for admission to hospital and ICU differed between pH1N1 and seasonal influenza. Older age was a greater risk factor for admission to hospital and ICU for pH1N1 and asthma was a greater risk factor for hospitalization for pH1N1. These results corroborate earlier research based on fewer cases from our institution[8] as well as a recent study from Colorado comparing children admitted to hospital with pH1N1 to those

with 2008-09 seasonal influenza A or B.[13] Conversely, underlying cardiac disease in those admitted to hospital and non-asthma chronic lung disease in those admitted to ICU were significantly more common in seasonal influenza. These results suggest that risk factors for new influenza strains and that high-risk groups during future pandemics may not be simply extrapolated from the experience with seasonal strains.

Guidelines from the Public Health Agency of Canada highlighted children less than 2 years of age as a high-risk group for pH1N1.[14] However, our results of a median age of 6.5 years in hospitalized pH1N1 patients is remarkably similar to studies from California[15] (median age 6 years) and Japan[16] (median age 7 years). While we found the proportion of hospitalized cases higher in older age categories in pH1N1, in the absence of community population-based epidemiologic data, we are not able to comment on any differences that may exist in age-specific attack, hospitalization, or ICU admission rates in our study population.

This study was not designed to identify the impact of differing management strategies on severity and outcomes of pH1N1. However, in contrast to the first study from our centre, in this study, differences in antiviral use between waves allowed for an interesting natural experiment. Overall, during the first wave, 0%, 46%, and 14% of children aged under 2 years, 2 to 4 years, and 5 years and over respectively received oseltamivir. During the second wave, 65%, 88%, and 86% of children under 2 years, 2 to 4 years, and 5 years and over respectively received antiviral therapy. While there was no difference in markers of disease severity including ICU admission, mechanical ventilation, and length of hospital stay between the two pandemic waves, there was a

greater need for oxygen in children hospitalized during wave 1. This difference only remained significant when restricting the analysis to those who did not receive antiviral therapy. This finding may reflect increased antiviral use directed at sicker children during wave 2, while the mildest cases did not receive antivirals.

In the previous analysis of the first wave of pH1N1 in Toronto, asthma was a more significant risk factor for pH1N1 than for seasonal influenza.[8] In this study, with more than 3 times the number of pH1N1 cases, we confirm the significance of asthma as a major risk factor; controlling for obesity and age (as a continuous variable) asthma was more likely to be present in hospitalized children with pH1N1 (OR 4.59, 95% CI 1.42-14.81 than with seasonal influenza A. In pH1N1 cases, asthma was associated with admission to ICU (OR 4.56, 95% CI 1.16-17.89). This is in contrast to seasonal influenza A in which underlying asthma was not significantly associated with ICU admission (OR 2.47, 95% CI 0.24-25.80). We did not find that the severity of asthma was differentially associated with hospitalization or ICU admission between pH1N1 and seasonal influenza. While 6 (19%) ICU admissions with pH1N1 had asthma (4 mild, 1 moderate, and 1 severe) compared to only 1 (3%) (mild) ICU admission with seasonal influenza, the numbers were too small to be able to demonstrate a difference. In a large California study of 345 children hospitalized or who died with pH1N1, 31% of hospitalized children and 34% of ICU and/or fatal cases had asthma.[15] In Japan, 14% of non-severe cases of pH1N1 and 47% of severe cases had asthma,[16] while a United Kingdom study found asthma was present in 16% of children <16 years and 31% of adults.[17] None of these studies examined severity of asthma or the differences between pH1N1 and seasonal

influenza.

Immunologic studies of severe pH1N1 cases have shown delayed expression of genes involved in the adaptive immune response, delayed viral clearance, and increased levels of innate immunity mediators involved in the Th1 and Th17 response.[18-19] Children with underlying asthma and other groups (such as pregnant women) thought to be at higher risk for severe pH1N1 disease[20-22] may have an altered immunologic and inflammatory response to this virus resulting in increased disease severity. Interleukin-5 (IL-5) has been shown to be highly expressed in bronchial mucosa of asthmatics,[23] is a key player in eosinophilic inflammation,[24] and has been found to be higher in serum of pH1N1 patients with pneumonia than those without.[25] However, further research is needed to fully understand this association. While there is some evidence in adults that adjuvant corticosteroids in severe pH1N1 may increase mortality,[26] the impact of inhaled corticosteroids in childhood asthma on pH1N1 severity is not known and this study was not designed nor powered to address this question.

Influenza vaccination coverage in asthmatic children has been poor in many countries.[27,28] Some physicians remain skeptical of the need for vaccinating all asthmatic children [29], while others tend to prioritize children with more severe asthma.[30] Definitive data has been elusive [31]. Our findings suggest that physicians should ensure all asthmatic children under their care have been vaccinated against pH1N1 (which is currently included in the standard seasonal influenza vaccine), regardless of severity of asthma, at least until randomized controlled trial data becomes available.

There are several limitations to this study including its retrospective design, single-center site, and inability to calculate population-based rates. The number of admitted patients with asthma, particularly to ICU, was small, and this may have hindered our ability to identify differences in risk based on severity. Additionally, we identified only the single most important underlying risk factor (with the exception of asthma, obesity, and age which were all collected for each patient) and thus, we were unable to explore interactions between risk factors in patients with multiple co-morbidities. Our metrics of influenza severity–ICU admission and duration of stay–may be impacted by non-medical factors such as bed availability. In regards to oxygen use, we did not have data on oximetry or criteria that were used by physicians to start or stop oxygen supplementation and thus it was difficult to determine the significance of the difference seen in wave 1 versus wave 2. In regards to oseltamivir use, we did not extract data on dosage, duration, or when the medication was begun. However, the use of oseltamivir in this study was at the discretion of the attending physician and thus reflective of 'real life' use. It is possible that we did not identify all patients at our hospital with influenza (seasonal or pH1N1) due to false negative testing or testing being performed at an outside hospital and not repeated at our institution; however, we expect both of these cases to be very rare.

CONCLUSION

Risk factors for severe disease, specifically the presence of underlying asthma and increased age, differed between pH1N1 and seasonal influenza in children. There

was no difference in overall disease severity. These results suggest that in future pandemics with new influenza strains, high-risk groups may be different than those traditionally considered as such. The reasons for the differing influence of asthma and age on host response to pH1N1 are not understood and further study of the underlying mechanisms contributing to these differences may shed new light on the host-pathogen immunobiology of a pandemic strain of influenza virus. This study emphasizes the need to ensure that all asthmatic children have been vaccinated against pH1N1 influenza, regardless of the severity of their asthma.

Characteristic	pH1N1 Wave 1 versus Wave 2			pH1N1 versus Seasonal Influenza		
	pH1N1 1st Wave	pH1N1 2nd Wave	p value	pH1N1 Total	Seasonal	p value
	n=58	n=118		n=176	n=200	
Sex, male, no. (%)	35 (60)	72 (61)	0.93	107 (61)	108 (54)	0.18
Age, yr, median (IQR)	6.4 (3.4-10.1)	6.5 (2.9-11.4)	0.81	**6.5 (3.0-10.6)**	**3.3 (1.4-7.8)**	**<0.01**
Age group, yr, no (%)						
<2	8 (14)	23 (19)	0.35	**31(18)**	**74(37)**	**<0.01**
2 to 5	13 (22)	24 (20)	0.75	37(21)	54(27)	0.18
>5	37 (64)	71 (60)	0.64	**108(61)**	**72(36)**	**<0.01**
Admitted to ICU						
No. (%) of children	12 (21)	20 (17)	0.36	32 (18)	31 (15)	0.49
Age, yr, median (IQR)	5.8 (3.2-7.3)	9.2 (5.4-11.4)	0.13	**7.3 (4.0-10.6)**	**3.6 (1.5-9.7)**	**0.02**
Required Mechanical Ventilation						
No. (%) of children	7 (12)	11 (9)	0.57	18 (10)	19 (10)	0.81
No. (%) of children admitted to ICU	7 (58)	11 (55)	0.85	18 (56)	19 (61)	0.69
Required Supplemental Oxygen						
No. (%) of children	26 (47)	33 (28)	0.013	59 (34)	n/a	n/a
Duration of Oxygen, d, median (IQR)	4 (2-6)	3(2-7)	0.73	3 (2-6)	n/a	n/a
Length of stay, d, median (IQR)						
In hospital	4 (2-6)	3 (2-5)	0.06	3 (2-5)	4 (2-7)	0.12
In ICU	3.5 (2.5-17)	2 (1.5-5)	0.08	3 (2-8)	2 (1-5)	0.24
Anti-viral therapy No. (%)	**11 (19)**	**97 (82)**	**<0.01**	**108 (61)**	**16 (8)**	**<0.01**

Table 1: Demographic and clinical characteristics of pH1N1 and seasonal influenza

	pH1N1 Symptoms				Seasonal Influenza Symptoms			
	0 to <2 yrs	2 to <5 yrs	>5 yrs	0 to 18 yrs	0 to <2 yrs	2 to <5 yrs	>5 yrs	0 to 18 yrs
Fever	31 (100)	36 (97)	99 (92)	166 (94)	64 (86)	45 (83)	59 (82)	168 (84)
Cough	29 (94)	34 (92)	84 (78)	147 (84)	34 (46)	29 (54)	39 (54)	102 (51)
Gastrointestinal	14 (45)	16 (43)	40 (37)	70 (40)	13 (15)	14 (26)	6 (8)	33 (16)
Wheeze	4 (13)	8 (22)	24 (22)	36 (20)	11 (15)	5 (9)	14 (19)	30 (15)
Pneumonia	11 (35)	12 (32)	29 (27)	52 (30)	9 (12)	8 (15)	19 (26)	36 (18)
Apnea	3 (10)	3 (8)	2 (2)	8 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Seizure	2 (7)	5 (14)	2 (2)	9 (5)	8 (11)	6 (11)	4 (6)	18 (9)
Encephalopathy	1 (3)	1 (3)	2 (2)	4 (2)	0 (0)	0 (0)	1 (14)	1 (0.5)
Myocarditis	0 (0)	1 (3)	1 (1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Myositis	0 (0)	0 (0)	2 (2)	2 (1)	0 (0)	1 (2)	0 (0)	1 (0.5)

Table 2: Clinical characteristics of pH1N1 and seasonal influenza by age category

Lab Value	pH1N1 influenza Number (%)	Seasonal influneza Number (%)
White blood cells ≥ 11.0 x 109/L	50 (29)	60 (31)
White blood cells < 4.0 x 109/L	33 (19%)	34 (17)
Absolute neutrophils >6.6 x 109/L	59 (35)	60 (31)
Absolute neutrophils <1.5 x 109/L	30 (18)	36 (19)
Absolute lymphocytes < 1.8 x 109/L	112 (66)	102 (53)

Table 3: Haematologic laboratory values for children admitted with pH1N1 and seasonal influenza.

Footnote: For pH1N1 influenza, 174 children had complete blood count and 170 had differential performed. For seasonal influenza, 196 children had complete blood count and 193 had differential performed.

Risk Factor	All Children Admitted to Hospital			Children Admitted to PICU		
	pH1N1 n=176	Seasonal n=200	p value	pH1N1 n=32	Seasonal n=31	p value*
Asthma	**26 (15)#**	**9 (5)**	**<0.01**	6 (19)	1 (3)	0.10
Mild Asthma	16(62)	7(78)	0.38	4(67)	1(100)	1.00
Moderate Asthma	6(23)	1(11)	0.44	1 (17)	0(0)	1.00
Severe Asthma	4 (15)	1(11)	0.75	1(17)	0(0)	1.00
Chronic Lung Disease	12 (7)	13 (7)	0.92	**0 (0)**	**5 (16)**	**0.02**
Obesity#	8(7)	14(9)	0.64	3 (20)	2 (9)	0.38
Cardiac Disease	**7 (4)**	**21 (11)**	**0.02**	3 (9)	4 (12)	0.71
Hemoglobinopathy	19 (11)	22 (11)	0.95	1 (3)	1 (3)	0.75
Immunodeficiency	32 (18)	42 (21)	0.49	1 (3)	2 (3)	0.61
Neurologic Impairment	21 (12)	26 (13)	0.76	6 (19)	8 (26)	0.56
Age <2 and no other risk factors	**16 (9)**	**35 (18)**	**0.02**	2 (6)	4 (13)	0.43

Table 4^: Risk factors for admission to hospital and intensive care unit, pandemic H1N1 versus seasonal influenza A

Footnotes: # Percentages in parentheses. *Fisher's exact test used when cell size is small. †Obesity was defined according to guidelines from the Centers for Disease Control as a body mass index ≥ 95th percentile for age in children older than 2 years.[32] Obesity could not be calculated for 45(31%) & 68(54%) children > 2 years in the seasonal and pH1N1 groups respectively. ^ Any differences between the numbers presented in Table 4 and those from O'Riordan et al. [8] are the result of a re-assessment of all pH1N1 and seasonal influenza cases for this study.

	pH1N1			Seasonal Influenza		
Risk Factor	OR	L95%CI	U95%CI	OR	L95%CI	U95%CI
Asthma	4.56	1.16	17.89	2.47	0.24	25.80
Obesity	4.18	0.76	22.95	1.06	0.20	5.64
Age 0 to <2 Years	1.00			1.00		
Age 2 to < 5 Years	1.70	0.30	9.48	1.40	0.44	4.44
Age >5 Years	0.89	0.19	4.07	0.62	0.19	1.98

Table 5: Multivariable regression of asthma, obesity, and age category as risk factors for ICU admission with pH1N1 and seasonal influenza A.

Footnote: ^ Asthma was also common as a risk factor (OR 8.77, 95% CI 1.85-41.52) for admission to hospital in pH1N1 compared to seasonal influenza (with age as continuous variable). Unadjusted (univariate) OR's for pH1N1: asthma (OR 1.43, 95% CI 0.52-3.91), obesity (OR 3.25, 95% CI 0.81-19.69), age 0 to <2 (OR 1.00), age 2 to <5 (OR 2.18, 95% CI 0.51-9.26), age >5 (OR 2.39, 0.66-8.58). Unadjusted (univariate) OR's for seasonal influenza: asthma (OR 0.67, 95% CI 0.08-5.56), obesity (OR 1.14, 95% CI 0.22-5.99), age 0 to <2 (OR 1.00), age 2 to <5 (OR 1.30, 95% CI 0.51-3.32), age >5 (OR 0.92, 95% CI 0.36-2.33).

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~~A retrospective cross sectional study of risk factors and clinical spectrum of children admitted to hospital with pandemic H1N1 influenza~~ A retrospective cross sectional study of risk factors and clinical spectrum of children admitted to hospital with pandemic H1N1 influenza as compared to influenza A

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ABSTRACT

Objective: To compare risk factors for severe disease admission to hospital and intensive care unit (ICU) and clinical outcomes in children with pandemic H1N1 (pH1N1) versus those with seasonal influenza.

Design: Retrospective analysis of children admitted to hospital with pH1N1 versus seasonal influenza A.

Setting: Canadian tertiary referral children's hospital.

Participants: All laboratory identified cases of pH1N1 in children under the age of 18 years admitted to hospital in 2009 (n=176) and all seasonal influenza cases admitted to hospital from influenza seasons 2004-05 to 2008-09 (n=200). Children with onset of symptoms more than 3 days after admission were excluded.

Primary and secondary outcome measures: Primary outcomes include admission to hospital and intensive care, need for mechanical ventilation, and presence of specific risk factors including age, asthma, and obesity. Secondary outcomes include length of stay in hospital, duration of supplemental oxygen requirement, and other demographic and clinical characteristics.

Results: Children admitted with pH1N1 were older than seasonal influenza A admissions (hospital admission: 6.5 vs 3.3 years, p<0.01; ICU admission: 7.3 vs 3.6 years, p=0.02). Children hospitalized pH1N1 were more likely to have a pre-existing diagnosis of asthma (15% vs 5%, p<0.01); however there was no difference in the severity of pre-existing asthma between the two groups. After controlling for obesity, asthma (OR 4.59, 95% CI 1.42-14.81) and age > 5 years (OR 2.87, 95% CI 1.60-5.16) were more common as risk

~~factors in admitted children with pH1N1. Asthma was a significant predictor of the need for intensive care in pH1N1 (OR 4.56, 95% CI 1.16-17.89) but not seasonal influenza A patients.~~

~~**Conclusion**: While most pH1N1 cases presented with classic influenza-like symptoms, risk factors for severe pH1N1 disease differed from seasonal influenza A. Older age and asthma were associated with increased admission to hospital and ICU for children with pH1N1.~~

Objective: To compare risk factors for severe disease, admission to hospital and intensive care unit (ICU), and other clinical outcomes in children with pandemic H1N1 (pH1N1) versus those with seasonal influenza.

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Primary and secondary outcome measures: Primary outcomes include admission to hospital and intensive care, need for mechanical ventilation. Secondary outcomes include length of stay in hospital and duration of supplemental oxygen requirement.

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asthma (15% vs 5%, p<0.01); however there was no difference in the severity of pre-existing asthma between the two groups. After controlling for obesity, asthma (OR 4.59, 95% CI 1.42-14.81) and age > 5 years (OR 2.87, 95% CI 1.60-5.16) were more common as risk factors in admitted children with pH1N1. Asthma was a significant predictor of the need for intensive care in pH1N1 (OR 4.56, 95% CI 1.16-17.89) but not seasonal influenza A patients.

Conclusion: While most pH1N1 cases presented with classic influenza-like symptoms, risk factors for severe pH1N1 disease differed from seasonal influenza A. Older age and asthma were associated with increased admission to hospital and ICU for children with pH1N1.

ARTICLE SUMMARY

Article focus

- Young age and underlying medical conditions have traditionally been considered risk factors for severe influenza in children.
- Children admitted with H1N1 influenza are more likely to have asthma, however, the impact of asthma severity is unknown.

Key messages

- The presence of asthma and increased age, but not severity of asthma, were more common as risk factors for hospitalization with severe H1N1 influenza than with seasonal influenza A.
- These results suggest that in future pandemics, certain high-risk groups may be more adversely affected than expected with seasonal influenza.
- Treatment of H1N1 influenza with oseltamivir did not appear to be associated with differing outcomes or severity of disease.

Strengths and limitations of this study

- The strength of this study is that it compares a large number of children admitted with microbiologically confirmed pH1N1 to those admitted over five years with seasonal influenza A. For each admitted child with suspected asthma, at least two physicians reviewed the case to confirm a diagnosis of pre-existing asthma and to grade the asthma as mild, moderate, or severe.
- The main limitations to this study include its retrospective design, single-center site, the inability to calculate population-based rates, and that the number of admitted patients with asthma, particularly to ICU, was small.

INTRODUCTION

~~In a large global pooled analysis of patients of all ages, the risk factors for severe pandemic H1N1 (pH1N1) disease have been found to have some notable differences from seasonal influenza including younger age, obesity, and pregnancy. [1] In the pediatric population, infants and young children have traditionally been considered at risk for severe seasonal influenza A.[2-3]~~ In a large global pooled analysis of patients of all ages, the risk factors for severe pandemic H1N1 (pH1N1) disease have been found to have some notable differences from seasonal influenza including younger age, obesity, and pregnancy.[1] In the pediatric population, infants and young children have traditionally been considered at risk for severe seasonal influenza A.[2-3] However, recently published pediatric studies suggest that while most cases of pH1N1 are relatively mild, older children, especially those suffering from asthma and obesity, may be at higher risk for severe disease. Rates of pediatric intensive care admission, mechanical ventilation, and mortality associated with pH1N1 may be higher than those

associated with seasonal influenza.[4-7]

A previous study from our center following the first wave of the pandemic found that children admitted with pH1N1 were significantly older and more likely to have asthma than those admitted with seasonal influenza A.[8] In late 2009, a second wave of pH1N1 resulted in more admissions to our hospital. The increase in pH1N1 cases allowed us to verify the findings of our initial study, and identify independent risk factors for admission to the intensive care unit (ICU) among pH1N1 and seasonal influenza hospitalized cases through multivariable analyses. Finally, we wanted to understand how differences in diagnostic methods and treatment between pH1N1 and seasonal influenza might affect outcomes. Thus our primary goals in this study were to compare the ageadjusted proportions of asthmatics among children admitted to hospital and the ICU with pH1N1 relative to those admitted with seasonal influenza, and determine whether age and asthma are independent predictors of ICU admission in pH1N1 as well as seasonal influenza infection. Secondary goals were to describe clinical features, other markers of illness severity, and effect of antiviral therapy and diagnostic methods on outcomes in children with pH1N1.

DESIGN

We identified and reviewed health records of all laboratory-confirmed cases of pH1N1 in children under the age of 18 years admitted in 2009 to The Hospital for Sick Children (SickKids), a large pediatric referral hospital in Toronto, Canada with over 14,000 admissions per year.[9] Cases were identified through a review of microbiology

labortatory records. We compared children admitted with pH1N1 to those admitted with seasonal influenza A during the 2004-2005 through 2008-2009 influenza seasons. In order to exclude potential hospital-acquired infections, we excluded any children ~~only children~~ who developed influenza-like symptoms on or after ~~prior to~~ the third day of admission. ~~were included in this study.~~ Testing was done at the clinical discretion of the attending physician. All patients with influenza-like illness were initially screened for influenza by direct immunofluorescence assay (DFA). During the first wave of the pandemic, all inpatient respiratory samples were tested using reverse transcription polymerase chain reaction (RT-PCR) with primers developed by the National Microbiology Laboratory, Winnipeg, Manitoba.[10] During the second wave, all inpatient respiratory samples were tested with a commercial real-time RT-PCR kit (RTPCR Kit 1.0, Astra Diagnostics, Hamburg). Seasonal influenza cases were identified through DFA and/or viral culture. Two physicians (MB and DT) reviewed each potential case of asthma to confirm the diagnosis and determine severity (Web Table). Any discrepancies were adjudicated by an asthma specialist (PS).

Comparisons were made between the pH1N1 and seasonal influenza A groups and between the first and second waves of pH1N1. Differences in normally distributed continuous variables were analyzed using Student's *t* test. Comparisons of skewed data (length of stay and age) were analyzed using non parametric Mann-Whitney and Kruskal-Wallis methods. The chi-square~~2~~ or Fisher's exact test was used to compare categorical variables between groups and as a test of heterogeneity among multiple proportions. We performed multivariable logistic regression to 1) adjust for the potential

confounding effect of age (as a continuous variable and categorical variable) on asthma as a risk factor in comparing the severity of pH1N1 and seasonal influenza; and 2) construct models of risk for ICU admission in pH1N1 and seasonal influenza A infection that included age (as a continuous variable and categorical variable), asthma, and obesity as independent variables. All statistical analysis was performed using Stata SE 10.[11]

SM and DT conceived of and designed the study, conducted the anlaysis, interpreted the data, and drafted the original manuscript. PP, MB, PS, SO, MB and UA contributed to the analysis and interpretation of data. All authors critically revised the article for important intellectual content and gave final approval of the version to be published. The SickKids Research Ethics Board approved and waived individual informed consent for this study.

RESULTS

179 children with pH1N1 were admitted in 2009 in two waves (May to July 2009 n=58, September to December 2009 n=118) (Figure 1), of whom 3 were excluded because the onset of symptoms was more than three days after admission. 200 children were admitted to hospital with seasonal influenza A over five seasons (2004-2005 n=46; 2005-2006 n=26; 2006-2007 n=36; 2007-2008 n=56; 2008-2009 n=36). There were no differences across the years of seasonal influenza cases in terms of demographic characteristics, underlying risk factors, or outcomes (data not shown).

Demographic Characteristics

Characteristics of children with pH1N1 and seasonal influenza are shown in Table 1. Children with pH1N1 were significantly older than those with seasonal influenza A (6.5 vs 3.3 years, p~~-value~~<0.01). The proportion of children over 5 years was higher in pH1N1 (61% vs 38%, p<0.01) whereas the proportion under 2 years was higher in seasonal influenza A (37% vs 18%, p<0.01). Children admitted to ICU with pH1N1 were older than those with seasonal influenza A (7.3 vs 3.6 years, p=0.02).

Disease Severity

Requirement and duration of oxygen therapy, ICU admission, mechanical ventilation and total length of hospital stay are shown in Table 1. 59 (34%) patients admitted with pH1N1 required oxygen supplementation. 32 (18%) children with pH1N1 required admission to ICU and of these, 18 (56%) required mechanical ventilation. There was no difference in ICU admission or need for mechanical ventilation between pH1N1 and seasonal influenza A. More children admitted during the first wave required oxygen than those admitted during the second wave (47% vs 28%, p=0.01). When examining only children who did not receive antiviral therapy, the difference in oxygen use between waves 1 and 2 remained significant (48% vs 19%, p=0.03). None of the pH1N1 patients died.

Clinical and Laboratory Characteristics

Most pH1N1 cases presented with fever and cough. More than one-third had

gastrointestinal symptoms (Table 2). The laboratory results of children admitted with pH1N1 are shown in Table 3. Four patients had positive blood cultures during their admission (*Streptococcus pneumoniae* (2), Viridans group *Streptococcus* (1), *Pseudomonas aerugenosa* (1)).

Risk Factors

Children with pH1N1 compared to those with seasonal influenza were more likely to have history of asthma (15% vs 5%, p<0.01); however, there was no difference in the severity of asthma between the two groups (Table 4). Cardiac disease (11% vs 4%, p=0.02) and age under 2 years with no other risk factors (18% vs 9%, p=0.02) were more common in children hospitalized with seasonal influenza. In patients requiring intensive care, history of asthma was more common in pH1N1 than in seasonal influenza A; however, this difference did not reach statistical significance (19% vs 3%, p=0.10). In a multivariable analysis including obesity, age category, and asthma, both age greater than 5 (with age <=2 as reference) (OR 2.87 95% CI 1.60-5.16) and history of asthma (OR 4.59, 95% CI 1.42-14.81) were more common as risk factors in admitted children with pH1N1 compared to seasonal influenza A. In the same analysis but using age as a continuous rather than categorical variable, asthma remained more common as a risk factor in pH1N1 (OR 8.77, 95% CI 1.85-41.52). Table 5 displays multivariable logistic regression analyses for predictors of ICU admission with pH1N1 and with seasonal influenza A infection. In multivariable models including obesity, age category and underlying asthma as independent variables, asthma was a significant predictor of the need for intensive care with pH1N1 infection (OR 4.56, 95% CI 1.16-17.89) but not with

seasonal influenza A infection. When the multivariable models included age as a continuous instead of categorical variable, underlying asthma remained a significant predictor of the need for ICU care with pH1N1 infection (OR 5.22, 95% CI 1.23-22.08). In children with asthma, 29% of those with pH1N1 versus 33% of those with seasonal influenza presented with acute wheeze (p=0.81). In children without underlying asthma, there was no difference in presentation with acute wheeze in those with pH1N1 (15%) and those with seasonal influenza (12%), p=0.51.

Diagnosis and Management

At our institution, seasonal influenza was diagnosed by DFA supplemented with viral culture whereas cases positive by DFA for pH1N1 required confirmation by PCR. To assess the potential impact of differing diagnostic methods, we re-analyzed all cases restricting solely to those positive by DFA. The only changes from the previously presented results were that the length of stay in hospital was longer in seasonal influenza (median 3.5 vs 3 days, p=0.03) and that underlying chronic lung disease (excluding asthma) was no longer significantly more common in those admitted to ICU with seasonal influenza A (p=0.09).

Children with pH1N1 were more likely to receive antiviral therapy (61% vs 8%, p<0.01). There were significant changes in how pH1N1 was managed between waves; 19% of children received antiviral therapy during wave 1 compared to 82% in wave 2 (p < 0.01). However, when comparing all children with pH1N1 who received antiviral therapy to those who did not, there were no significant differences in the need for ICU

admission (22% vs 14%, p=0.07), mechanical ventilation (14% vs 8%, p=0.08), or length of stay in hospital (median duration 3 days vs 3 days, p=0.68). To test if sicker children received antiviral therapy, we compared all available Canadian Triage and Acuity Scores[12] (CTAS), a standardized measure of disease acuity, between pH1N1 patients who did (n=65), and did not (n=42) receive antiviral therapy and did not find a significant difference between the two groups (p=0.70).

DISCUSSION

Most cases of pH1N1 presented with a classic influenza-like illness, with no convincing evidence that pH1N1 was more severe than seasonal influenza. However, the risk factors for admission to hospital and ICU differed between pH1N1 and seasonal influenza. Older age was a greater risk factor for admission to hospital and ICU for pH1N1 and asthma was a greater risk factor for hospitalization for pH1N1. These results corroborate earlier research based on fewer cases from our institution[8] as well as a recent study from Colorado comparing children admitted to hospital with pH1N1 to those with 2008-09 seasonal influenza A or B.[13] Conversely, underlying cardiac disease in those admitted to hospital and non-asthma chronic lung disease in those admitted to ICU were significantly more common in seasonal influenza. These results suggest that risk factors for new influenza strains and that high-risk groups during future pandemics may not be simply extrapolated from the experience with seasonal strains.

Guidelines from the Public Health Agency of Canada highlighted children less than 2 years of age as a high-risk group for pH1N1.[14] However, our results of a median age of 6.5 years in hospitalized pH1N1 patients is remarkably similar to studies from

California[15] (median age 6 years) and Japan[16] (median age 7 years). While we found the proportion of hospitalized cases higher in older age categories in pH1N1, in the absence of community population-based epidemiologic data, we are not able to comment on any differences that may exist in age-specific attack, hospitalization, or ICU admission rates in our study population.

This study was not designed to identify the impact of differing management strategies on severity and outcomes of pH1N1. However, in contrast to the first study from our centre, in this study, differences in antiviral use between waves allowed for an interesting natural experiment. Overall, during the first wave, 0%, 46%, and 14% of children aged under 2 years, 2 to 4 years, and 5 years and over respectively received oseltamivir. During the second wave, 65%, 88%, and 86% of children under 2 years, 2 to 4 years, and 5 years and over respectively received antiviral therapy. While there was no difference in markers of disease severity including ICU admission, mechanical ventilation, and length of hospital stay between the two pandemic waves, there was a greater need for oxygen in children hospitalized during wave 1. This difference only remained significant when restricting the analysis to those who did not receive antiviral therapy. This finding may reflect increased antiviral use directed at sicker children during wave 2, while the mildest cases did not receive antivirals.

In the previous analysis of the first wave of pH1N1 in Toronto, asthma was a more significant risk factor for pH1N1 than for seasonal influenza.[8] In this study, with more than 3 times the number of pH1N1 cases, we confirm the significance of asthma as

a major risk factor; controlling for obesity and age (as a continuous variable) asthma was more likely to be present in hospitalized children with pH1N1 (OR 4.59, 95% CI 1.42-14.81 than with seasonal influenza A. In pH1N1 cases, asthma was associated with admission to ICU (OR 4.56, 95% CI 1.16-17.89). This is in contrast to seasonal influenza A in which underlying asthma was not significantly associated with ICU admission (OR 2.47, 95% CI 0.24-25.80). We did not find that the severity of asthma was differentially associated with hospitalization or ICU admission between pH1N1 and seasonal influenza. While 6 (19%) ICU admissions with pH1N1 had asthma (4 mild, 1 moderate, and 1 severe) compared to only 1 (3%) (mild) ICU admission with seasonal influenza, the numbers were too small to be able to demonstrate a difference. In a large California study of 345 children hospitalized or who died with pH1N1, 31% of hospitalized children and 34% of ICU and/or fatal cases had asthma.[15] In Japan, 14% of non-severe cases of pH1N1 and 47% of severe cases had asthma,[16] while a United Kingdom study found asthma was present in 16% of children <16 years and 31% of adults.[17] None of these studies examined severity of asthma or the differences between pH1N1 and seasonal influenza.

Immunologic studies of severe pH1N1 cases have shown delayed expression of genes involved in the adaptive immune response, delayed viral clearance, and increased levels of innate immunity mediators involved in the Th1 and Th17 response.[18-19] Children with underlying asthma and other groups (such as pregnant women) thought to be at higher risk for severe pH1N1 disease[20-22] may have an altered immunologic and inflammatory response to this virus resulting in increased disease severity. Interleukin-5

(IL-5) has been shown to be highly expressed in bronchial mucosa of asthmatics,[23] is a key player in eosinophilic inflammation,[24] and has been found to be higher in serum of pH1N1 patients with pneumonia than those without.[25] However, further research is needed to fully understand this association. While there is some evidence in adults that adjuvant corticosteroids in severe pH1N1 may increase mortality,[26] the impact of inhaled corticosteroids in childhood asthma on pH1N1 severity is not known and this study was not designed nor powered to address this question.

Influenza vaccination coverage in asthmatic children has been poor in many countries.[27,28] Some physicians remain skeptical of the need for vaccinating all asthmatic children [29], while others tend to prioritize children with more severe asthma.[30] Definitive data has been elusive [31]. Our findings suggest that physicians should ensure all asthmatic children under their care have been vaccinated against pH1N1 (which is currently included in the standard seasonal influenza vaccine), regardless of severity of asthma, at least until randomized controlled trial data becomes available.

There are several limitations to this study including its retrospective design, single-center site, and inability to calculate population-based rates. The number of admitted patients with asthma, particularly to ICU, was small, and this may have hindered our ability to identify differences in risk based on severity. Additionally, we identified only the single most important underlying risk factor (with the exception of asthma, obesity, and age which were all collected for each patient) and thus, we were unable to explore interactions between risk factors in patients with multiple co-

morbidities. Our metrics of influenza severity–ICU admission and duration of stay–may be impacted by non-medical factors such as bed availability. In regards to oxygen use, we did not have data on oximetry or criteria that were used by physicians to start or stop oxygen supplementation and thus it was difficult to determine the significance of the difference seen in wave 1 versus wave 2. In regards to oseltamivir use, we did not extract data on dosage, duration, or when the medication was begun. However, the use of oseltamivir in this study was at the discretion of the attending physician and thus reflective of 'real life' use. It is possible that we did not identify all patients at our hospital with influenza (seasonal or pH1N1) due to false negative testing or testing being performed at an outside hospital and not repeated at our institution; however, we expect both of these cases to be very rare.

CONCLUSION

Risk factors for severe disease, specifically the presence of underlying asthma and increased age, differed between pH1N1 and seasonal influenza in children. There was no difference in overall disease severity. These results suggest that in future pandemics with new influenza strains, high-risk groups may be different than those traditionally considered as such. The reasons for the differing influence of asthma and age on host response to pH1N1 are not understood and further study of the underlying mechanisms contributing to these differences may shed new light on the host-pathogen immunobiology of a pandemic strain of influenza virus. This study emphasizes the need to ensure that all asthmatic children have been vaccinated against pH1N1 influenza, regardless of the severity of their asthma.

	pH1N1 Wave 1 versus Wave 2			pH1N1 versus Seasonal Influenza		
Characteristic	pH1N1 1st Wave	pH1N1 2nd Wave	p value	pH1N1 Total	Seasonal	p value
	n=58	n=118		n=176	n=200	
Sex, male, no. (%)	35 (60)	72 (61)	0.93	107 (61)	108 (54)	0.18
Age, yr, median (IQR)	6.4 (3.4-10.1)	6.5 (2.9-11.4)	0.81	**6.5 (3.0-10.6)**	**3.3 (1.4-7.8)**	**<0.01**
Age group, yr, no (%)						
<2	8 (14)	23 (19)	0.35	**31(18)**	**74(37)**	**<0.01**
2 to 5	13 (22)	24 (20)	0.75	37(21)	54(27)	0.18
>5	37 (64)	71 (60)	0.64	**108(61)**	**72(36)**	**<0.01**
Admitted to ICU						
No. (%) of children	12 (21)	20 (17)	0.36	32 (18)	31 (15)	0.49
Age, yr, median (IQR)	5.8 (3.2-7.3)	9.2 (5.4-11.4)	0.13	**7.3 (4.0-10.6)**	**3.6 (1.5-9.7)**	**0.02**
Required Mechanical Ventilation						
No. (%) of children	7 (12)	11 (9)	0.57	18 (10)	19 (10)	0.81
No. (%) of children admitted to ICU	7 (58)	11 (55)	0.85	18 (56)	19 (61)	0.69
Required Supplemental Oxygen						
No. (%) of children	26 (47)	33 (28)	0.013	59 (34)	n/a	n/a
Duration of Oxygen, d, median (IQR)	4 (2-6)	3(2-7)	0.73	3 (2-6)	n/a	n/a
Length of stay, d, median (IQR)						
In hospital	4 (2-6)	3 (2-5)	0.06	3 (2-5)	4 (2-7)	0.12
In ICU	3.5 (2.5-17)	2 (1.5-5)	0.08	3 (2-8)	2 (1-5)	0.24
Anti-viral therapy No. (%)	**11 (19)**	**97 (82)**	**<0.01**	**108 (61)**	**16 (8)**	**<0.01**

Table 1: Demographic and clinical characteristics of pH1N1 and seasonal influenza

	pH1N1 Symptoms				Seasonal Influenza Symptoms			
	0 to <2 yrs	2 to <5 yrs	>5 yrs	0 to 18 yrs	0 to <2 yrs	2 to <5 yrs	>5 yrs	0 to 18 yrs
Fever	31 (100)	36 (97)	99 (92)	166 (94)	64 (86)	45 (83)	59 (82)	168 (84)
Cough	29 (94)	34 (92)	84 (78)	147 (84)	34 (46)	29 (54)	39 (54)	102 (51)
Gastrointestinal	14 (45)	16 (43)	40 (37)	70 (40)	13 (15)	14 (26)	6 (8)	33 (16)
Wheeze	4 (13)	8 (22)	24 (22)	36 (20)	11 (15)	5 (9)	14 (19)	30 (15)
Pneumonia	11 (35)	12 (32)	29 (27)	52 (30)	9 (12)	8 (15)	19 (26)	36 (18)
Apnea	3 (10)	3 (8)	2 (2)	8 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Seizure	2 (7)	5 (14)	2 (2)	9 (5)	8 (11)	6 (11)	4 (6)	18 (9)
Encephalopathy	1 (3)	1 (3)	2 (2)	4 (2)	0 (0)	0 (0)	1 (14)	1 (0.5)
Myocarditis	0 (0)	1 (3)	1 (1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Myositis	0 (0)	0 (0)	2 (2)	2 (1)	0 (0)	1 (2)	0 (0)	1 (0.5)

Table 2: Clinical characteristics of pH1N1 and seasonal influenza by age category

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Lab Value	pH1N1 influenza Number (%)	Seasonal influneza Number (%)
White blood cells ≥ 11.0 x 109/L	50 (29)	60 (31)
White blood cells < 4.0 x 109/L	33 (19%)	34 (17)
Absolute neutrophils >6.6 x 109/L	59 (35)	60 (31)
Absolute neutrophils <1.5 x 109/L	30 (18)	36 (19)
Absolute lymphocytes < 1.8 x 109/L	112 (66)	102 (53)

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Table 3: Haematologic laboratory values for children admitted with pH1N1 and seasonal influenza.

Footnote: For pH1N1 influenza, 174 children had complete blood count and 170 had differential performed. For seasonal influenza, 196 children had complete blood count and 193 had differential performed.

Risk Factor	All Children Admitted to Hospital			Children Admitted to PICU		
	pH1N1 n=176	Seasonal n=200	p value	pH1N1 n=32	Seasonal n=31	p value*
Asthma	**26 (15)#**	**9 (5)**	**<0.01**	6 (19)	1 (3)	0.10
Mild Asthma	16(62)	7(78)	0.38	4(67)	1(100)	1.00
Moderate Asthma	6(23)	1(11)	0.44	1 (17)	0(0)	1.00
Severe Asthma	4 (15)	1(11)	0.75	1(17)	0(0)	1.00
Chronic Lung Disease	12 (7)	13 (7)	0.92	**0 (0)**	**5 (16)**	**0.02**
Obesity#	8(7)	14(9)	0.64	3 (20)	2 (9)	0.38
Cardiac Disease	**7 (4)**	**21 (11)**	**0.02**	3 (9)	4 (12)	0.71
Hemoglobinopathy	19 (11)	22 (11)	0.95	1 (3)	1 (3)	0.75
Immunodeficiency	32 (18)	42 (21)	0.49	1 (3)	2 (3)	0.61
Neurologic Impairment	21 (12)	26 (13)	0.76	6 (19)	8 (26)	0.56
Age <2 and no other risk factors	**16 (9)**	**35 (18)**	**0.02**	2 (6)	4 (13)	0.43

Table 4^: Risk factors for admission to hospital and intensive care unit, pandemic H1N1 versus seasonal influenza A

Footnotes: # Percentages in parentheses. *Fisher's exact test used when cell size is small. †Obesity was defined according to guidelines from the Centers for Disease Control as a body mass index ≥ 95$_{th}$ percentile for age in children older than 2 years.[32] Obesity could not be calculated for 45(31%) & 68(54%) children > 2 years in the seasonal and pH1N1 groups respectively. ^ Any differences between the numbers presented in Table 4 and those from O'Riordan et al. [8] are the result of a re-assessment of all pH1N1 and seasonal influenza cases for this study.

	pH1N1			Seasonal Influenza		
Risk Factor	OR	L95%CI	U95%CI	OR	L95%CI	U95%CI
Asthma	4.56	1.16	17.89	2.47	0.24	25.80
Obesity	4.18	0.76	22.95	1.06	0.20	5.64
Age 0 to <2 Years	1.00			1.00		
Age 2 to < 5 Years	1.70	0.30	9.48	1.40	0.44	4.44
Age >5 Years	0.89	0.19	4.07	0.62	0.19	1.98

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Table 5: Multivariable regression of asthma, obesity, and age category as risk factors for ICU admission with pH1N1 and seasonal influenza A.

Footnote: ^ Asthma was also common as a risk factor (OR 8.77, 95% CI 1.85-41.52) for admission to hospital in pH1N1 compared to seasonal influenza (with age as continuous variable). Unadjusted (univariate) OR's for pH1N1: asthma (OR 1.43, 95% CI 0.52-3.91), obesity (OR 3.25, 95% CI 0.81-19.69), age 0 to <2 (OR 1.00), age 2 to <5 (OR 2.18, 95% CI 0.51-9.26), age >5 (OR 2.39, 0.66-8.58). Unadjusted (univariate) OR's for seasonal influenza: asthma (OR 0.67, 95% CI 0.08-5.56), obesity (OR 1.14, 95% CI 0.22-5.99), age 0 to <2 (OR 1.00), age 2 to <5 (OR 1.30, 95% CI 0.51-3.32), age >5 (OR 0.92, 95% CI 0.36-2.33).

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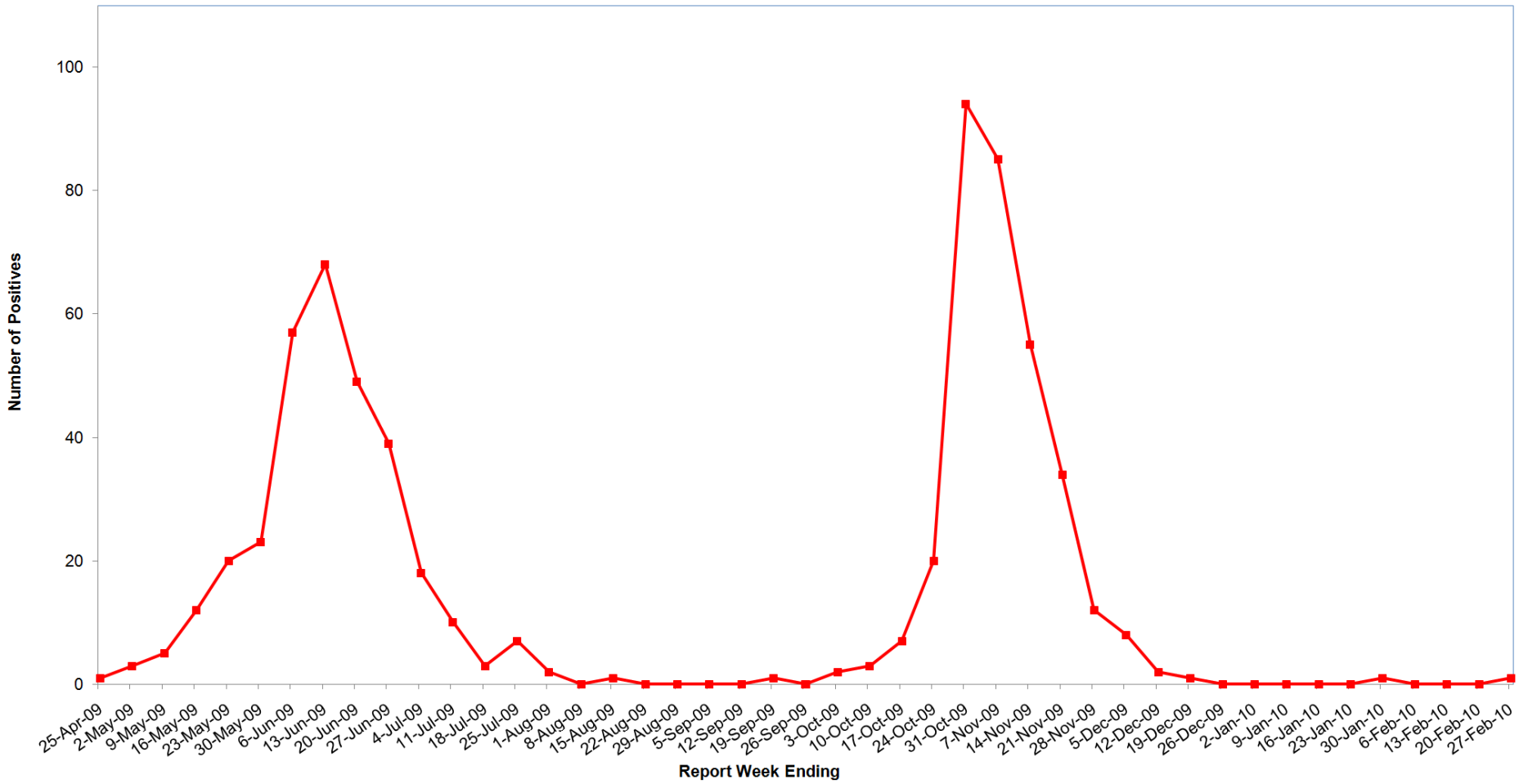

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1**X**	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2**X**	Explain the scientific background and rationale for the investigation being reported
Objectives	3 **X**	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 **X**	Present key elements of study design early in the paper
Setting	5 **X**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 **X**	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7 **X**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* **X**	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 **X**	Describe any efforts to address potential sources of bias
Study size	10 **X**	Explain how the study size was arrived at
Quantitative variables	11 **X**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 **X**	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13* **X**	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* **X**	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15* **X**	Report numbers of outcome events or summary measures
Main results	16 **X**	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 **X**	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18 **X**	Summarise key results with reference to study objectives
Limitations	19 **X**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 **X**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 **X**	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 **X**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.