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Original Article

Pandemic (H1N1) 2009 influenza in Canadian pediatric cancer and hematopoietic stem cell transplant patients

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Background The impact of pandemic H1N1 influenza (pH1N1) virus in pediatric cancer is uncertain. The objectives of this study were to characterize the clinical course of pH1N1 and identify factors associated with severe outcomes.

Methods We conducted a Canadian multicenter retrospective review of children with cancer and stem cell transplant (SCT) recipients who were diagnosed with laboratory-confirmed pH1N1 infection between May 1, 2009 and January 31, 2010.

Results We identified 100 (19 in wave 1 and 81 in wave 2) cases of pH1N1 infection. Median age was 8·7 years. 71% had a hematologic malignancy, and 20% received SCT. Median duration of fever and illness was 2 and 12·5 days, respectively. 51 (51·5%) were hospitalized for a median of 5 days, with no deaths and only 1 requiring admission to the intensive care unit. Radiologically confirmed pneumonia was diagnosed in 10 (10%). Interruption of chemotherapy or conditioning occurred in 43 patients. In multivariable analyses, age <5 years (relative to ≥10 years) and neutropenia were associated with hospitalization while neutropenia was associated with pneumonia. Despite oseltamivir use in 89%, viral shedding was prolonged (median, 46 days) and often persisted after symptom resolution. However, an extended treatment course (>5 days) correlated with shortened duration of viral shedding ($P = 0{\cdot}041$).

Conclusions pH1N1 infection in pediatric cancer and SCT patients infrequently caused complications but commonly interrupted cancer treatment. Persistent shedding of virus after illness resolution was common. Further research is needed to verify this finding as it could have implications for treatment guidelines and infection control practices.

Keywords cancer, child, pandemic H1N1 influenza, stem cell transplant.

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Introduction

First detected in April of 2009,[1] the pandemic H1N1 influenza (pH1N1) virus rapidly spreads globally, triggering the first pandemic of the 21st century. By August 1, 2010, more than 214 countries reported laboratory-confirmed cases to the World Health Organization, including over 18 449 deaths.[2]

Children with cancer and pediatric hematopoietic stem cell transplant (SCT) recipients comprise an important group of immunocompromised patients in whom prolonged viral shedding and serious influenza-associated morbidity are common.[3–10] If pH1N1 substantially contributes to future influenza seasons as may be expected via antigenic drift, an understanding of its clinical course and severity in pediatric cancer patients in multiple geographic regions would help inform healthcare needs, provide information to facilitate decision-making regarding cancer treatment interruption, and identify early interventions to improve outcomes.

An analysis of pooled surveillance data on laboratory-confirmed pH1N1 cases from 19 countries or administrative regions demonstrated that the odds ratio (OR) for death given hospitalization was >5 for immunocompromised patients, but did not determine ORs for subgroups of these patients.[11] Several studies of pH1N1 infection in pediatric cancer patients have yielded conflicting information, with some demonstrating a mild course,[12–15] while a

Brazilian study documented a high mortality rate among hospitalized cases.[16] Almost all of these studies were conducted at single centers, thus raising concerns about the generalizability of findings.

Consequently, we conducted a Canadian multicenter retrospective analysis of pH1N1 in pediatric cancer. Our objectives were to describe the clinical course and identify factors associated with severe outcomes of children with cancer or pediatric SCT recipients diagnosed with laboratory-confirmed pH1N1.

Methods

Patients and setting

We identified eligible cases through retrospective review of virology reports and health records from a base population of patients cared for by the Divisions of Haematology/Oncology at six Canadian pediatric referral centers (BC Children's Hospital, Vancouver; The Children's Hospital of Winnipeg, Winnipeg; Children's Hospital London Health Sciences Centre, London; McMaster Children's Hospital, Hamilton; The Hospital for Sick Children, Toronto; and Children's Hospital of Eastern Ontario, Ottawa).

Subjects eligible for study inclusion were (i) ≤18 years of age; (ii) receiving or about to receive chemotherapy for cancer or conditioning for SCT, or received treatment within the preceding 3 months (for chemotherapy patients), 6 months (for autologous SCT recipients), 2 years (for allogeneic SCT recipients), or receiving immunosuppressive therapy for graft-versus-host disease for those ≥2 years post-allogeneic SCT; and (iii) diagnosed with pH1N1 infection by RT-PCR [using primers developed by the Centers for Disease Control and Prevention (CDC; Atlanta, GA)[17] or the National Microbiology Laboratory (NML; Public Health Agency of Canada, Winnipeg, MB),[18] or the Astra influenza Screen & Type (Astra Diagnostics, Hamburg, Germany)[19]] of nasopharyngeal or flocked nasal mid-turbinate swabs between May 1, 2009 and January 6, 2010.

Case details abstracted from health records were reported on a standardized case report form. We collected patient demographics, underlying conditions, treatment information, clinical manifestations, pandemic H1N1 vaccination history, antiviral and antibiotic use, level of care required and influenza-related complications. All centers obtained research ethics board approval for the study.

Outcomes and definitions

North America experienced two waves of pH1N1 activity, peaking in most locations around June and October 2009.[20] Based on reporting of laboratory-confirmed pH1N1 hospitalized cases and deaths to the Public Health Agency of Canada, we defined wave 1 as the period prior to August 30, 2009.[21]

Severe outcomes examined were hospitalization, radiologically confirmed pneumonia (defined as new pulmonary infiltrate on chest imaging associated with compatible clinical symptoms), intensive care unit (ICU) admission, need for mechanical ventilation, and mortality. Potential predictors of severe outcomes were identified from the literature or based on clinical experience and were defined *a priori*. Other complications of interest that developed between symptom onset and resolution were classified as respiratory complications, extra-respiratory complications or microbiologically confirmed infections. Extra-respiratory complications were further subcategorized into hematologic or non-hematologic complications. Hematologic complications of interest were neutropenia (absolute neutrophil count $<500/mm^3$), lymphopenia ($<500/mm^3$), and thrombocytopenia ($<50\,000/mm^3$). Non-hematologic complications specifically sought for included clinical diagnoses of sepsis (hypotension requiring fluid bolus or inotrope administration), pericarditis/myocarditis, myositis (elevated creatine phosphokinase), encephalitis, and hepatitis (aspartate aminotransferase or alanine aminotransferase > twice the upper limit of normal for age).

Obesity and underweight were covariates of interest and were examined for children at least 2 years of age. Obesity was defined as a body mass index (BMI) ≥ 95th percentile, and underweight was defined as BMI < 5th percentile based on the gender- and age-specific BMI reference from Centers for Disease Control and Prevention.[22] Children <2 years were not included in this analysis because of uncertainty in how to categorize children in this age-group.

Reflecting the recommendations of the Advisory Committee on Immunization Practices,[23] full vaccination with pH1N1 vaccine for children 6 months to <9 years was defined as receipt of two vaccine doses separated by at least 4 weeks with dose 2 received ≥14 days prior to illness onset. Those who received only one dose ≥14 days before illness onset were classified as partially vaccinated. Children aged 9–18 years were considered fully vaccinated with receipt of one vaccine dose ≥14 days prior to illness onset.

Statistical considerations

Standard descriptive statistics were used to summarize data on the study population. For all statistical testing, only the first pH1N1 episode was included in cases with multiple episodes within the same child because these episodes cannot be considered independent. Comparisons of data categorized by hospitalization versus no hospitalization, presence or absence of radiologically confirmed pneumonia, and pandemic wave (wave 2 versus 1) were made using the Mann–Whitney test for continuous variables and the χ^2 or Fisher's exact test as appropriate for categorical variables. We performed univariate and multivariable linear or logistic regression, as appropriate, to adjust for potential

confounding variables and to identify independent predictors of severe outcomes. We considered for the multivariable models all variables with P values <0·1 in univariate analysis and retained in the final model all variables with an adjusted P-value <0·05. All tests were two-sided, and a P value <0·05 was considered statistically significant. Data were analyzed by spss statistical software (version 16·0, SPSS Inc, Chicago, IL, USA).

Results

We identified a total of 102 episodes of laboratory-confirmed pH1N1 infection in 100 children with 100 unique first episodes. Unique episodes were distributed in two distinct waves: 19 in wave 1 prior to August 29, 2009, and 81 in wave 2 from August 30, 2009 onward. In total, 51/99 were hospitalized (information missing in one child) and 10/100 were diagnosed with radiologically confirmed pneumonia.

Patient characteristics

Patient characteristics are illustrated in Table 1, and results are stratified by whether children required hospitalization or was diagnosed with pneumonia. Median age was 8·7 years, and males comprised 58·0% of cases. Cancer diagnoses at the time of pH1N1 infection were leukemia (63·0%), solid tumor (22·0%), lymphoma (8·0%), and brain tumor (7·0%). Of these patients, 4 (4·0%) had refractory disease, 12 (12·0%) had relapsed disease, and 2 (2·0%) had a secondary malignancy. 82 (82·0%) were receiving chemotherapy around the time of pH1N1 infection, and 20 (20·0%) had undergone either autologous (n = 8) or allogeneic (n = 12) SCT. Obesity was documented in 21/98 children ≥2 years, while two children were classified as underweight. Corticosteroids were part of anticancer therapy in 38 (38·0%) patients. Of 18 children who received pH1N1 vaccine in the second wave, only one was fully vaccinated at the onset of pH1N1 illness.

Table 1. Patient characteristics

	Overall (n = 100)	Hospitalized (n = 51)*	Not hospitalized (n = 48)*	P	Pneumonia (n = 10)	No pneumonia (n = 90)	P
Male gender	58 (58·0)	30 (58·8)	27 (56·2)	0·796	6 (60·0)	52 (57·8)	1·000
Age, y, median (IQR)	8·7 (5·0–13·0)	6·5 (4·3–10·4)	10·6 (6·0–15·2)	**0·003**	7·2 (5·9–9·8)	8·8 (4·6–13·2)	0·527
Age-group				**0·008**			**0·050**
0–4 years	25 (25·0)	18 (35·3)	6 (12·5)		1 (10·0)	24 (26·7)	
5–9 years	35 (35·0)	19 (37·3)	16 (33·3)		7 (70·0)	28 (31·1)	
≥10 years	40 (40·0)	14 (27·5)	26 (54·2)		2 (20·0)	38 (42·2)	
Cancer diagnosis				0·128			0·712
Leukemia	63 (63·0)	27 (52·9)	36 (75·0)		6 (60·0)	57 (63·3)	
Lymphoma	8 (8·0)	6 (11·8)	2 (4·2)		0 (0·0)	8 (8·9)	
Solid tumor	22 (22·0)	14 (27·5)	7 (14·6)		3 (30·0)	19 (21·1)	
Brain tumor	7 (7·0)	4 (7·8)	3 (6·2)		1 (10·0)	6 (6·7)	
Stem cell transplant				0·373			–
Autologous	8 (8·0)	6/12 (50·0)	2/8 (25·0)		0 (0·0)	8/20 (38·1)	
Allogeneic	12 (12·0)	6/12 (50·0)	6/8 (75·0)		0 (0·0)	12/20 (60·0)	
Any comorbidity	12 (12·0)	7 (13·7)	5 (10·4)	0·614	1 (10·0)	11 (12·2)	1·000
Asthma or chronic lung disease	6 (6·0)	4 (7·8)	2 (4·2)	0·679	1 (10·0)	5 (5·6)	0·478
Obesity (excludes children <2 years)	21/98 (21·4)	10/49 (20·4)	10/48 (20·8)	0·959	1/10 (10·0)	20/88 (22·7)	0·684
ANC <500/mm^3 at pH1N1 diagnosis	26/93 (28·0)	22/49 (44·9)	4/43 (9·3)	**<0·001**	7 (70·0)	19 (22·9)	**0·004**
Receiving corticosteroids	38 (38·0)	17 (33·3)	21 (43·8)	0·287	4 (40·0)	34 (37·8)	1·000
pH1N1 vaccination	(n = 79)	(n = 41)	(n = 37)	0·678	(n = 10)	(n = 69)	0·569
Fully or partially vaccinated	6 (7·6)	4 (9·8)	2 (5·4)		1 (10·0)	5 (7·2)	
Not vaccinated**	73 (92·4)	37 (90·2)	35 (94·6)		9 (90·0)	64 (92·8)	
Early antiviral therapy							
(within 24 hours)***	36/85 (42·4)	16/44 (36·4)	20/40 (50·0)	0·207	4/10 (40·0)	32/75 (42·7)	0·873
(within 48 hours)***	49/85 (57·6)	22/44 (50·0)	27/40 (67·5)	0·104	4/10 (40·0)	45/75 (60·0)	0·229

Data are n (%) unless otherwise indicated. ANC, absolute neutrophil count. Bold values in tables indicate P-values lower than the significance level α = 0.05.

*Indicates that hospitalization status was not available for one child.

**Includes vaccination received after or <14 days prior to onset of illness.

***From symptom onset to treatment initiation.

Table 2. Clinical manifestations at presentation and during the course of the influenza illness

	At presentation (n = 100)		During illness (n = 100)	
	n	%	*n*	%
Fever	84	84·0	88	88·0
Maximum temperature, °C, mean (SD)	38·8 (0·6)		38·9 (0·7)	
Rhinorrhea	46	46·0	46	46·0
Sore throat	22	22·0	26	26·0
Cough	80	80·0	85	85·0
Hemoptysis	0	0·0	1	1·0
Wheezing	3	3·0	6	6·0
Respiratory distress	2	2·0	4	4·0
Rash	6	6·0	7	7·0
Headache	13	13·0	15	15·0
Myalgia	12	12·0	13	13·0
Abdominal symptoms*	24	24·0	28	28·0
Fatigue	20	20·0	26	26·0
Irritability	3	3·0	3	3·0
Altered level of consciousness	1	1·0	1	1·0
Seizure	0	0·0	0	0·0

*Includes nausea and/or vomiting and/or diarrhea.

Clinical presentation, course, and management

Table 2 illustrates symptoms at presentation of pH1N1 and during the illness course. The most commonly reported presenting symptoms were fever (84·0%) and cough (80·0%); 24·0% had abdominal pain, nausea, vomiting, and/or diarrhea. Median interval between symptom onset and clinical encounter was 1 day [interquartile range (IQR), 0–2].

The treatment and clinical course of pH1N1 infection are presented in Tables 1 and 3. Antiviral therapy was prescribed to most patients during the pandemic, with more frequent antiviral use in wave 2 than 1 (P = 0·001). Overall, antiviral therapy was extended beyond the standard 5-day course for 17 (19·5%) patients, 12 of whom received a 10-day course. Antibiotics were given in 56 (56·0%) cases. Median duration of symptoms (defined as the interval between onset of any symptom and resolution of all symptoms) and that of fever was 12·5 and 2 days, respectively.

We were able to determine the duration of shedding of pH1N1 virus for 35 patients, the median of which was 46 days. In the 22 patients for whom both duration of symptoms and viral shedding were available, 13 continued to shed virus after symptom resolution. The median duration of viral shedding did not differ significantly based on whether or not the patient was hospitalized (63 days [IQR, 14–88·5] versus 44 days [IQR, 19–78·5]; P = 0·986) or diagnosed with pneumonia (65·5 days [IQR, 20·25–95·75] versus 44 days [IQR, 14–85]; P = 0·836). The median duration of viral shedding was, however, significantly shorter in wave 2 of the pandemic (38 days [IQR, 13–70] versus 98.5 days [IQR, 28.25–157.25]; P = 0·034). As antiviral use differed between wave 1 and 2, we explored the possible confounding effects of different aspects of antiviral prescription (antiviral treatment versus no treatment, antiviral treatment within 24 hours versus after 24 hours of symptom onset, extended versus standard antiviral course) and other factors on the logarithm of length of viral shedding in linear regression analyses (Table 4). After multiple regression analysis, we found that an extended antiviral treatment course, but not wave 2, was significantly associated with shortened duration of viral shedding.

In terms of other complications, 2 experienced asthma exacerbation. Upper respiratory tract disease associated with pH1N1 infection were otitis media (n = 4), sinusitis (n = 2), and croup (n = 1). Hematologic abnormalities were neutropenia (n = 32), lymphopenia (n = 29), and thrombocytopenia (n = 17). Of the 11 patients classified as having a non-hematologic, extra-respiratory complication, nine had hepatitis. Microbiologically confirmed bacterial infection was documented in two cases (one coagulase-negative staphylococcus bacteremia and one *Staphylococcus aureus* cellulitis). Infection with a herpes group virus during the pH1N1 illness was reported in two patients (one herpes simplex virus and one Epstein–Barr virus), both managed as outpatients. Of the 82 patients scheduled for chemotherapy or conditioning for SCT, 43 had their chemotherapy or conditioning delayed (n = 23), modified (n = 5), or stopped/canceled (n = 11).

Severe outcomes of pH1N1

As previously described, 51 children were hospitalized and 10 had radiologically confirmed pneumonia (Table 3). The median duration of hospitalization was 5 days (IQR, 3-13 days); for those with absolute neutrophil count (ANC) < 500 cells/mm^3 at pH1N1 diagnosis, it was 6 days (IQR, 4–11·5 days). Overall, few patients developed critical illness. There was no mortality; one child was admitted to ICU for pneumonia requiring ≥60% supplemental oxygen and continuous positive airway pressure by face mask but not intubation or mechanical ventilation; and one child had pneumonia resulting in ≥60% supplemental oxygen therapy but did not require ICU admission.

Table 5 displays univariate and multivariable analyses for predictors of pH1N1-associated hospitalization and pneumonia. In univariate analyses, children <5 years were more likely to be hospitalized (P = 0·003) and those aged 5–9 years trended toward being more likely to have pneumonia (P = 0·063), compared to children ≥10 years. Neutropenia at pH1N1 diagnosis was associated with

Table 3. Clinical course, treatment, and complications

	Overall (*n* = 100)	Wave 1 (*n* = 19)	Wave 2 (*n* = 81)	*P*
Clinical course and management				
Days of symptoms, median (IQR)	12·5 (6–18)	18 (7–19·25)	10 (6–16·75)	0·149
Days of fever, median (IQR)	2 (1–4)	2 (1–3)	2 (1–4)	0·443
Days of viral shedding, median (IQR)	46 (14–85)	98·5 (28·25–157·25)	38 (13–70)	**0·034**
Antiviral therapy	89 (89·0)	12 (63·2)	77 (95·1)	**0·001**
Early antiviral therapy				
Within 24 hours of symptom onset	36/85 (42·4)	2/11 (18·2)	34/74 (45·9)	0·108
Within 48 hours of symptom onset	49/85 (57·6)	6/11 (54·5)	43/74 (58·1)	1·000
Antiviral duration				
Standard (5 days)	70/87 (80·5)	8/11 (72·7)	62/76 (81·6)	0·443
Extended (>5 days)	17/87 (19·5)	3/11 (27·3)	14/76 (18·4)	
Antibiotic treatment	56 (56·0)	9 (47·4)	47 (58·0)	0·400
Oxygen supplementation	4 (4·0)	2 (10·5)	2 (2·5)	0·162
Respiratory complications*	9 (9·0)	1 (5·3)	8 (9·9)	1·000
Upper respiratory tract	7 (7·0)	1	6	
Asthma exacerbation	2 (2·0)	0	2	
Extra-respiratory complications	39 (39·0)	8 (42·1)	31 (38·3)	0·758
Hematologic	50 (50·0)	13	37	
Non-hematologic	11 (11·0)	5	6	
Laboratory-confirmed infections	5 (5·0)	1 (5·3)	4 (4·9)	1·000
Bacterial	2 (2·0)	0	2	
Fungal	1 (1·0)	1	0	
Viral	2 (2·0)	0	2	
Alteration of chemotherapy**	43/82 (52·42)	9/17 (52·9)	34/65 (52·3)	0·963
Severe outcomes				
Hospitalization	51/99 (51·5)	10 (52·6)	41/80 (51·2)	0·914
Duration, d, median (IQR)	5 (3–13)	8 (4–68·5)	5 (3–10·75)	0·143
Pneumonia***	10 (10·0)	2 (10·5)	8 (9·9)	1·000
ICU admission†	1 (1·0)	0 (0·0)	1 (1·2)	1·000
Need for mechanical ventilation	0 (0·0)	–	–	–
Death	0 (0·0)	–	–	–

Data are *n* (%) unless otherwise indicated. Bold values in tables indicate P-values lower than the significance level $\alpha = 0.05$.
*Excludes radiologically confirmed pneumonia.
**Denominators exclude patients not scheduled for chemotherapy.
***Radiologically confirmed.
†None required ventilation, inotropes, dialysis, or extracorporeal membrane oxygenation.

hospitalization ($P < 0·001$) and pneumonia ($P = 0·005$), as was neutropenia detected at any time during the illness ($P < 0·001$ and $P = 0·015$, respectively). We did not collect data on lymphopenia at pH1N1 diagnosis, but lymphopenia detected at any time during the illness was not associated with hospitalization or pneumonia. Multiple logistic regression revealed that age category and neutropenia (both at diagnosis and during the illness) were significant independent predictors of hospitalization, with children <5 years at highest risk. Neutropenia, but not age, was a significant predictor of pneumonia in multiple logistic regression analysis. The models that included age and neutropenia at diagnosis fit the observed data well (Hosmer–Lemeshow $P = 0·955$ and 0·778 for hospitalization and pneumonia, respectively) and discriminated well between those who were and were not hospitalized [c-index, 0·767 (95% CI, 0·670–0·864)] as well as between children with and without pneumonia [c-index, 0·839 (95% CI, 0·735–0·942)].

Discussion

This study resulted in several important observations. First, pH1N1 infection was uncomplicated in most children with cancer although commonly interrupted anticancer therapy. Second, neutropenia was an important predictor of hospitalization as well as pneumonia. Third, antiviral prescription increased significantly during wave 2 of the pandemic. Finally, prolonged viral shedding often persisted after symptom resolution, and an extended antiviral treatment

Table 4. Duration of viral shedding and potential predictive factors

	Log_{10} (days of viral shedding)			
	Univariate analysis		Multivariable analysis	
	Coefficient β (SE)	*P*	Coefficient β (SE)	*P*
Male gender	−0·07 (0·16)	0·685	–	–
Age (years)	−0·01 (0·02)	0·578	–	–
Receiving corticosteroids	0·13 (0·17)	0·441	–	–
ANC < 500/mm^3 at diagnosis of pH1N1	0·13 (0·21)	0·529	–	–
ALC < 500/mm^3 during illness course	−0·03 (0·18)	0·893	–	–
Fully or partially vaccinated	−0·19 (0·36)	0·600	–	–
Hospitalized versus not hospitalized	−0·03 (0·16)	0·857	–	–
Pneumonia versus no pneumonia	0·05 (0·25)	0·837	–	–
Pandemic wave (wave 2 versus 1)	−0·35 (0·18)	0·059	−0·25 (0·20)	0·219
Antiviral therapy	−0·26 (0·25)	0·304	–	–
Early antiviral therapy				
Within 24 hours of symptom onset	0·04 (0·18)	0·809	–	–
Within 48 hours of symptom onset	0·05 (0·17)	0·754	–	–
Antiviral duration (extended versus standard)	−0·36 (.017)	**0·048**	−0·37 (0·17)	**0·041**

ALC, absolute lymphocyte count. Bold values in tables indicate P-values lower than the significance level $\alpha = 0.05$.

course >5 days was associated with shortened length of viral shedding.

In our cohort, 51·5% of patients were hospitalized and 10% developed lower respiratory tract infection. Although only one patient was admitted to the ICU and none died, 52·4% of those scheduled for chemotherapy or conditioning had treatment modified or held. These results are comparable to those of modest-sized case series of pediatric cancer patients from Italy,[13] Texas,[12] Jordan,[14] and Turkey.[15] In contrast, a Brazilian study found that 8/14 pediatric cancer patients hospitalized with pH1N1 required ICU admission and ventilator support. This is consistent with the high rate of severe complications from pH1N1 infection in the general Brazilian population.[16] Potential explanations for the discrepant findings of this study include increased predisposition to severe pH1N1 infection in the Brazilian population owing to host genetic and/or socioeconomic factors.

Several factors may contribute to the generally favorable outcome of pH1N1 infection in cancer patients. First, parents of children with cancer are likely to seek prompt medical attention in the presence of fever, resulting in early diagnosis and antiviral treatment. A meta-analysis of 11 randomized controlled trials (RCTs) showed that oseltamivir treatment was associated with a reduced risk of lower respiratory tract complications in adolescents and adults with flu symptoms.[24] A recent RCT demonstrated that early antiviral treatment in children aged 1–3 years reduced illness duration and incidence of otitis media.[25] Second, increased cytokine and chemokine plasma levels have been shown to be markers of critical illness with pH1N1 infection, suggesting that immunopathology may contribute to disease severity.[26,27] It is possible that the relatively benign course of illness in children with cancer is partly related to decreased cytokine and chemokine production related to immune suppression. Third, high levels of cross-reacting but non-neutralizing antibodies that result from previous seasonal influenza exposures, leading to immune complex-mediated pulmonary disease, have been advanced as a novel biological mechanism of severe cases of pH1N1 in middle-aged individuals.[28] Pediatric cancer and SCT patients have impaired serum antibody responses to both seasonal influenza vaccination and natural infection and would, therefore, likely be protected from this mechanism of severe pH1N1 disease. Finally, concurrent bacterial infection has been documented in 29% of lung tissue specimens from fatal human cases of pH1N1.[29] Neutropenia was an independent predictor of pneumonia in our study, and neutropenia, in association with fever, would trigger hospitalization and broad-spectrum antibiotic therapy resulting in early treatment of established or subclinical bacterial lower respiratory tract infection along with more intensive supportive therapy.

It is possible that neutropenia was merely a surrogate for profound lymphopenia that has been shown to correlate with the risk of influenza-associated lower respiratory tract infection [30,31] and that the lack of association of concurrent lymphopenia with pneumonia in our study reflected a higher cut-off point compared to previous studies demonstrating association (<500/mm^3 versus <100–200/mm^3).[30,31] More detailed analysis of ANC and absolute lymphocyte count (ALC) in relation to the pattern of radiographic changes (viral versus bacterial) in future studies could provide further insight. In addition to neutropenia, our study indicated that younger age (particularly those <5 years) was associated with hospitalization for pH1N1 infection. This is consistent with reported rates of pH1N1-associated hospitalization in the general pediatric population, being highest for children <5 years and especially for those <12 months.[32] Morbid obesity has been associated with hospitalization and death from pH1N1 infection in

Table 5. Factors associated with hospitalization and radiologically confirmed pneumonia

	Hospitalization				Pneumonia			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age-group*		**0·010**		**0·041**		0·078		0·086
0–4 years	5·6 (1·8–17·2)	**0·003**	4·9 (1·4–17·1)	**0·012**	0·8 (0·1–9·2)	0·852	0·5 (0·04–6·7)	0·626
5–9 years	2·2 (0·9–5·6)	0·095	2·2 (0·7–6·2)	0·155	4·8 (0·9–24·6)	0·063	4·4 (0·8–25·4)	0·099
≥10 years	Reference	–	Reference	–	Reference	–	Reference	–
ANC <500/mm^3 at pH1N1 diagnosis	7·9 (2·5–25·7)	**<0·001**	8·1 (2·4–27·1)	**0·001**	7·9 (1·9–33·4)	**0·005**	9·2 (2·0–42·1)	**0·004**
ANC <500/mm^3 during illness course	6·8 (2·4–18·9)	**<0·001**	7·0 (2·4–20·4)	**<0·001**	5·9 (1·4–24·8)	**0·015**	6·4 (1·4–28·2)	**0·015**
ALC <500/mm^3 during illness course	1·5 (0·6–3·5)	0·401	–	–	1·6 (0·4–6·2)	0·495	–	–

ORs generated by logistic regression.
ANC, absolutely neutrophil count; ALC, absolute lymphocyte count; CI, confidence interval; OR, odds ratio.
*ORs and *P* values displayed in multivariable models are those generated with inclusion of ANC <500/mm^3 at pH1N1 diagnosis as a predictor variable. Bold values in tables indicate P-values lower than the significance level $\alpha = 0.05$

adults.[33,34] In contrast, in children, hospitalization appears to be associated with being underweight, and death has not been associated with BMI category.[33] Consistent with this observation was the relatively uncomplicated clinical course of our cohort, which included a large number of obese but only two underweight children.

While antiviral treatment was prescribed to most patients in our study, its use was significantly less frequent during wave 1, when only 63·2% were treated with oseltamivir. This occurred despite the existence of antiviral therapy guidelines predating the pandemic that recommended treatment for children at high risk of severe influenza, including those with cancer.[35,36] The gap in adherence to such guidelines during wave 1 suggests that either guideline dissemination was suboptimal or that clinicians were further risk-stratifying patients for antiviral therapy. The increased use of antivirals during wave 2 in our cohort might have reflected emergence of reports in the literature and media of severe pH1N1 cases.

Our study demonstrated that cancer and SCT patients had prolonged viral shedding, which has also been observed in studies of cancer patients with seasonal influenza.[37] A recent report of cancer patients hospitalized with pH1N1 also documented prolonged excretion of virus, in which 5/10 mechanically ventilated patients shed virus for ≥11 days.[16] Given that severe respiratory illness has also been associated with delayed pH1N1 clearance,[38] the authors acknowledged that they could not determine whether the persistent pH1N1 shedding in their study was attributed to the severity of pH1N1 disease, the underlying immunocompromised state, or both. Our data indicate that an immunocompromised state is an important contributor to prolonged excretion of pH1N1 virus. Therefore, pH1N1-infected cancer patients could potentially serve as mixing vessels, when infected with seasonal influenza viruses, for genetic reassortment and generation of a more virulent influenza subtype.[39]

Another important observation was that viral shedding often extended far beyond the symptomatic period. This finding may have important infection control implications. While isolation of the symptomatic patient is clear, the role of asymptomatic viral shedding in transmission is less well studied and recommendations for isolation of these patients are variable.[40,41] If asymptomatic shedding can result in the spread of influenza, then it would be important to practice strict infection control practices until laboratory confirmation of viral clearance in hospitalized patients and for outpatients returning to the ambulatory clinic for continuing care regardless of symptoms.

We also found that treatment with an extended course of oseltamivir was associated with a shorter duration of viral shedding. While early use of oseltamivir has been associated with reduction in days of viral shedding,[38] we are not aware of previous data demonstrating a correlation between length of antiviral treatment and duration of viral shedding. Some experts have advocated a 10-day course as the standard duration for immunocompromised patients[42] although the Advisory Committee on Immunization Practices merely states that 'longer treatment regimens might be necessary in severely ill hospitalized patients or persons with immunosuppression'.[43] These factors, along with the generally mild clinical course, may have accounted for the

infrequent use of extended antiviral treatment in the study. Our findings, if confirmed in future studies, would lend further support to a recommendation for longer treatment regimens and may have beneficial infection control implications. However, any potential benefits from prolonged antiviral therapy would have to be balanced against the risk of selection for resistance mutations.[44]

Limitations of the study include its retrospective design and inability to calculate population-based rates. Based on its retrospective nature, our ability to determine whether the hematologic complications were attributable to influenza infection or to chemotherapy was limited, and our results may be affected by unobserved confounders or insufficient adjustment for observed confounders. The precision in our estimate of the duration of viral shedding may have been limited given that follow-up influenza testing was performed at the clinicians' discretion. The extent of prolonged viral shedding may have been overestimated by overrepresentation of serial sampling in patients with longer courses. We did not capture data on the duration of individual symptoms and therefore were not able to identify those which could potentially be used to guide optimal retesting and treatment. Although larger than previous studies of pediatric cancer and SCT patients, our sample size was still relatively small. Some of our metrics of influenza severity such as hospitalization, length of hospital stay, and ICU admission may be influenced by variation in clinical practice across centers as well as non-medical factors such as publicity surrounding the pandemic and bed availability.

In conclusion, pH1N1 infection was associated with an uncomplicated course in most pediatric cancer and SCT patients but commonly altered scheduling of chemotherapy or transplant conditioning. Although neutropenia was an independent predictor of radiologically confirmed pneumonia, it is unclear whether it can be used as a criterion separate from lymphopenia for decision-making regarding cancer treatment modification given the limitations in our analysis of lymphopenia as a risk factor. Despite the uncomplicated course in most, viral shedding was prolonged and often continued after symptom resolution. Prospective studies evaluating the effects of extended antiviral treatment on viral shedding in cancer and SCT patients, while addressing the limitations in this study, could have an important bearing on infection control practices and treatment guidelines.

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Conflict of interest

The authors have no commercial or other association that might pose a conflict of interest.

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References

1 Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S *et al.* Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009; 361:680–689.
2 World Health Organization. Pandemic (H1N1) 2009 – update 104. Available at: http://www.who.int/csr/don/2010_06_11/en/index.html (Accessed 21 June 2010 [cited 2010 21 June]: Available from: http://www.who.int/csr/don/2010_06_11/en/index.html).
3 Maltezou HC, Kafetzis DA, Abisaid D, Mantzouranis EC, Chan KW, Rolston KV. Viral infections in children undergoing hematopoietic stem cell transplant. Pediatr Infect Dis J 2000; 19:307–312.
4 Kempe A, Hall CB, MacDonald NE *et al.* Influenza in children with cancer. J Pediatr 1989; 115:33–39.
5 Christensen MS, Nielsen LP, Hasle H. Few but severe viral infections in children with cancer: a prospective RT-PCR and PCR-based 12-month study. Pediatr Blood Cancer 2005; 45:945–951.
6 Lujan-Zilbermann J, Benaim E, Tong X, Srivastava DK, Patrick CC, DeVincenzo JP. Respiratory virus infections in pediatric hematopoietic stem cell transplantation. Clin Infect Dis 2001; 33:962–968.
7 Feldman S, Webster RG, Sugg M. Influenza in children and young adults with cancer: 20 cases. Cancer 1977; 39:350–353.
8 Moore DL, Vaudry W, Scheifele DW *et al.* Surveillance for influenza admissions among children hospitalized in Canadian immunization monitoring program active centers, 2003–2004. Pediatrics 2006; 118:e610–e619.
9 Roberts A, Bitnun A, McGeer A *et al.* Laboratory-confirmed influenza-associated hospitalizations among children in the metropolitan Toronto and Peel region by active surveillance, 2004–2005. Can Commun Dis Rep 2006; 32:203–207.
10 Quach C, Piche-Walker L, Platt R, Moore D. Risk factors associated with severe influenza infections in childhood: implication for vaccine strategy. Pediatrics 2003; 112:e197–e201.
11 Van Kerkhove MD, Vandemaele KA, Shinde V *et al.* Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med 2011; 8:e1001053.
12 Cost C, Brock E, Adams-Huet B, Siegel JD, Ardura MI. 2009 pandemic influenza A (H1N1) virus infection in pediatric oncology and hematopoietic stem cell transplantation patients. Pediatr Blood Cancer 2011; 56:127–133.
13 Caselli D, Carraro F, Castagnola E *et al.* Morbidity of pandemic H1N1 influenza in children with cancer. Pediatr Blood Cancer 2010; 55:226–228.
14 Amayiri N, Madanat F. Retrospective analysis of pediatric cancer patients diagnosed with the pandemic H1N1 influenza infection. Pediatr Blood Cancer 2011; 56:86–89.
15 Ozdemir N, Celkan T, Midilli K *et al.* Novel influenza a (H1N1) infection in a pediatric hematology oncology clinic during the 2009-2010 pandemia. Pediatr Hematol Oncol 2011; 28:288–293.

16 Souza TM, Salluh JI, Bozza FA *et al.* H1N1pdm influenza infection in hospitalized cancer patients: clinical evolution and viral analysis. PLoS ONE 2010; 5:e14158.

17 Dawood FS, Jain S, Finelli L *et al.* Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009; 360:2605–2615.

18 Cutler J, Schleihauf E, Hatchette TF *et al.* Investigation of the first cases of human-to-human infection with the new swine-origin influenza A (H1N1) virus in Canada. CMAJ 2009; 4:159–163.

19 Petrich A, Luinstra K, Chong S, Mahony JB, Smieja M. Performance comparison of commercial molecular assays to detect and identify pandemic influenza A in a sensitivity panel and in clinical specimens (abstract). 26th Clinical Virology Symposium. 2010 April 25–28:S35.

20 Zimmer SM, Crevar CJ, Carter DM, *et al.* Seroprevalence following the second wave of pandemic 2009 H1N1 influenza in Pittsburgh, PA, USA. PLoS One 2010; 5:e11601.

21 Helferty M, Vachon J, Tarasuk J, Rodin R, Spika J, Pelletier L. Incidence of hospital admissions and severe outcomes during the first and second waves of pandemic (H1N1) 2009. CMAJ 2010; 182:1981–1987.

22 Kuczmarski RJ, Ogden CL, Grummer-Strawn LM *et al.* CDC growth charts: United States. Adv Data 2000; 8:1–27.

23 Litchfield SM. Summary recommendations by the advisory committee on immunization practices (ACIP) for the use of H1N1 influenza vaccine for the 2009–2010 vaccination season. AAOHN J 2009; 57:354.

24 Hernan MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomized clinical trials. Clin Infect Dis 2011; 53:277–279.

25 Heinonen S, Silvennoinen H, Lehtinen P *et al.* Early oseltamivir treatment of influenza in children 1–3 years of age: a randomized controlled trial. Clin Infect Dis 2010; 51:887–894.

26 To KK, Hung IF, Li IW *et al.* Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. Clin Infect Dis 2010; 50:850–859.

27 Hagau N, Slavcovici A, Gonganau DN *et al.* Clinical aspects and cytokine response in severe H1N1 influenza A virus infection. Crit Care 2010; 14:R203.

28 Monsalvo AC, Batalle JP, Lopez MF *et al.* Severe pandemic 2009 H1N1 influenza disease due to pathogenic immune complexes. Nat Med 2010; 17:195–199.

29 Centers for Disease Control and Prevention. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) – United States, May–August 2009. MMWR Morb Mortal Wkly Rep 2009; 58:1071–1074.

30 Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2004; 39:1300–1306.

31 Chemaly RF, Ghosh S, Bodey GP *et al.* Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. Medicine 2006; 85:278–287.

32 Louie JK, Acosta M, Winter K *et al.* Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 2009; 302:1896–1902.

33 Morgan OW, Bramley A, Fowlkes A *et al.* Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. PLoS ONE 2010; 5:e9694.

34 Louie JK, Acosta M, Samuel MC *et al.* A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). Clin Infect Dis 2011; 52:301–312.

35 American Academy of Pediatrics Committee on Infectious Diseases. Antiviral therapy and prophylaxis for influenza in children. Pediatrics 2007; 119:852–860.

36 Harper SA, Bradley JS, Englund JA *et al.* Seasonal influenza in adults and children – diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the infectious diseases society of America. Clin Infect Dis 2009; 48:1003–1032.

37 McMinn P, Carrello A, Cole C, Baker D, Hampson A. Antigenic drift of influenza A (H3N2) virus in a persistently infected immunocompromised host is similar to that occurring in the community. Clin Infect Dis 1999; 29:456–458.

38 Meschi S, Selleri M, Lalle E *et al.* Duration of viral shedding in hospitalized patients infected with pandemic H1N1. BMC Infect Dis 2011; 11:140.

39 Schrauwen EJ, Herfst S, Chutinimitkul S *et al.* Possible increased pathogenicity of pandemic (H1N1) 2009 influenza virus upon reassortment. Emerg Infect Dis 2011; 17:200–208.

40 Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control 2007; 35(10 Suppl 2):S65–S164.

41 Ontario Agency for Health Protection and Promotion, Provincial Infectious Diseases Advisory Committee. Routine Practices and Additional Precautions in All Health Care Settings. Toronto, ON: Queen's Primer for Ontario, 2011.

42 Casper C, Englund J, Boeckh M. How I treat influenza in patients with hematologic malignancies. Blood 2010; 115:1331–1342.

43 Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM. Antiviral agents for the treatment and chemoprophylaxis of influenza – recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep [Practice Guideline]. 2011; 60:1–24.

44 Memoli MJ, Hrabal RJ, Hassantoufighi A, Eichelberger MC, Taubenberger JK. Rapid selection of oseltamivir- and peramivir-resistant pandemic H1N1 virus during therapy in 2 immunocompromised hosts. Clin Infect Dis 2010; 50:1252–1255.