Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec, Canada

Rodica Gilca,^{a,b} Gaston De Serres,^{a,b} Nicole Boulianne,^a Najwa Ouhoummane,^a Jesse Papenburg,^c Monique Douville-Fradet,^a Élise Fortin,^a Marc Dionne,^a Guy Boivin,^c Danuta M. Skowronski^d

^aQuebec National Institute of Public Health, Quebec City, QC, Canada. ^bLaval University, QC, Canada. ^cResearch Center in Infectious Diseases, CHUQ-CHUL, QC, Canada. ^dBC Centre for Disease Control, Vancouver, BC, Canada.

Correspondence: Rodica Gilca, MD, PhD, Institut National de Santé Publique du Québec, 2400 d'Estimauville, Quebec, QC G1E 7G9, Canada.
E-mail: rodica.gilca@ssss.gouv.qc.ca

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Background/Objective This case-control study was carried out to estimate risk factors associated with hospitalizations and severe outcomes [intensive care unit (ICU) admission or death] among patients with illness because of laboratory-confirmed 2009 pandemic A/H1N1 virus (pH1N1) during the first wave of pH1N1 activity in the province of Quebec, Canada.

Patients/Methods We collected epidemiologic information by phone using a standardized questionnaire from patients with laboratory-confirmed pH1N1 illness during the first spring/summer pandemic wave in Quebec, Canada. Risk factors associated with hospitalization were assessed by comparing hospitalized to community cases and for ICU admission or death through comparison with hospitalized cases.

Results Cases (321 hospitalized patients including 47 ICU admissions and 15 deaths) were compared to controls (395 non-hospitalized patients) by using multivariable logistic regression adjusted for gender, age, education, being a health care worker,

smoking, seasonal influenza vaccination, delay to consultation, antiviral use before admission, pregnancy, underlying medical conditions, and obesity. Age <5 years, underlying medical conditions (neuromuscular, cardiac, pulmonary, and renal conditions, diabetes, asthma, and other), and delayed consultation were associated with hospitalization. The strongest association with hospitalization was observed for neuromuscular disorders. Antiviral medication before hospital admission protected against severe disease. Association of obesity with hospitalization was not significant after adjustment in multivariable analysis. Among hospitalized patients, age ≥60 years and immune suppression were associated with death.

Conclusions Previously identified risk factors for seasonal influenza were also associated with increased risk of severe pH1N1 outcomes. The independent role of obesity needs to be further defined.

Keywords Influenza, hospitalizations, endemic, risk factors.

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Introduction

As with seasonal influenza, the vast majority of patients with illness caused by the 2009 pandemic A/H1N1 virus (pH1N1) experienced an uncomplicated course to recovery. Similar to previous pandemics, the median age of patients presenting with pH1N1 was younger than that of patients with seasonal influenza.¹ Surveillance reports, outbreak investigations, descriptive case series, and a few case-control studies have attempted to characterize the profile of patients experiencing more severe outcomes.^{1–17} The estimated rate of hospitalization among symptomatic patients with pH1N1 varied by age, ranging from 0–53% in children 5–17 years of age, 2–19% in children <5 years of age,¹⁸ and up to 4–0% in adults.¹ Among hospitalized cases, between 6% and 31% were admitted to the intensive care unit

(ICU) and up to 5% died.^{2,5,11,17} Secondary bacterial infections have been confirmed in 20–43% of severe cases.^{4,5,19,20}

Most patients with severe pH1N1 illness had underlying medical conditions known also to increase the risk for complications from seasonal influenza.^{2–5,19,21,22} Obesity, which was not previously recognized as a risk factor for severe influenza, has been observed in a substantial proportion of patients with severe pH1N1 illness.^{2,3,5,6,10,19} Two recent studies comparing hospitalizations and deaths from pH1N1 with the source population suggested that obesity may be independently associated with severe outcomes because of pH1N1.^{23,24}

We conducted a case-control study to assess risk factors associated with hospitalization and severe outcomes (ICU admission or death) among patients with confirmed

pH1N1 illness during the first pandemic wave in the province of Quebec, Canada.

Methods

Population

In the province of Quebec, Canada (population 7.8 million; the second largest provincial population in Canada), all respiratory specimens from patients with suspected pH1N1 infection between April 16th and July 1st, 2009, attending primary care clinics or any hospital were collected and sent to the provincial reference laboratory for testing, along with basic demographic information on patients. Beginning in July, testing protocols changed in the province of Quebec such that only patients attending designated sentinel sites or admitted to hospital were offered laboratory testing for pH1N1 and five additional laboratories were designated to conduct testing. Specimens were tested by reverse transcription polymerase chain reaction (RT-PCR). A positive result by both RT-PCR assays targeting the pH1N1 M and HA genes was required for laboratory confirmation. All hospitalized and non-hospitalized cases with onset of disease during the study period and included in the confirmed case registry of the provincial reference laboratory were considered eligible for the study. A separate provincial registry for patients hospitalized with confirmed pH1N1 infection including name of the hospital and underlying medical conditions was used to validate information related to hospitalization through the admitting hospitals and public health departments of the four regions included in the study. Patients with laboratory-confirmed pH1N1 illness admitted to a hospital for ≥ 24 hours were eligible as cases. Severe disease was defined as admission to ICU and/or death. Controls were non-hospitalized patients with laboratory-confirmed pH1N1 illness.

Study period and data collection

The study period was from May 25th to July 1st, a period that includes approximately 80% of the confirmed cases detected during the first wave of pH1N1 activity in Quebec (Figure 1). During that period, specific diagnostic testing was well established, almost all cases were indigenous, i.e., unrelated to international travel, and laboratory-confirmed case ascertainment was consistent. The study was conducted in the four most affected regions (Montreal, Montérégie, Laval, and Quebec City), which accounted for 78% of all hospitalized and 83% of all non-hospitalized cases in the province of Quebec. Trained interviewers called eligible patients between July 17th and August 10th and collected demographic and clinical data using a standardized questionnaire. For children under 14 years, the respondents were parents. For deceased patients, the respondents were close family relatives. The number of non-hospitalized cases was planned to be proportional to the number of hospitalized cases for each region. For patients with discrepancies in the data, public health departments contacted the relevant hospital and returned corrected validated data to the study team, as well as to the provincial registry.

This study was carried out as an emergency outbreak investigation under the legal mandate of the provincial Chief Medical Officer, and no research ethics board approval was sought.

Statistical analysis

Proportions were compared using chi-square test or Fisher exact test when appropriate; distributions of age were compared with Wilcoxon rank sum non-parametric test. Odds ratios (OR) to identify risk factors for hospitalization and severe disease were derived by univariate and multivariable unconditional logistic regression. The lowest risk of death was observed in the <5 and in the 5–19 year age groups

Figure 1. Non-hospitalized and hospitalized pH1N1 cases in the province of Quebec during the period of April 16–August 30, 2009.

(Table 1). Because the <5 year age group has a high risk for hospitalization and complications for seasonal influenza, we wanted to assess the impact of the pH1N1 virus specifically on this age group. Consequently, the 5–19 age group was selected as the reference category. Underlying medical conditions were analyzed as a group (≥ 1 underlying medical condition) or individually for the most frequent categories (cardiac, pulmonary, diabetes mellitus, asthma, immunosuppression, neurological, and renal conditions). Other underlying conditions (e.g., anemia, cancer, liver, and metabolic diseases) were merged into the 'other conditions' category. Obesity was defined as a body mass index (BMI) ≥ 30 kg/m² for adults ≥ 18 years and as a BMI ≥ 95 th percentile for children 2–18 years.²⁵ In adults, morbid obesity was defined as a BMI ≥ 40 kg/m². Indicator variables were created for non-applicable values (e.g., pregnancy for <14 or ≥ 50 year-old-woman, or man; obesity for <2-year-old; smoking in <14-year-old; health care workers in <20- or >65-year-old); as well as for variables with missing values (Table 1). Variables significantly associated with the outcomes of interest in univariate analysis (with a $P < 0.05$) or known as potential confounders (gender, seasonal influenza vaccination, antiviral therapy before admission, and pregnancy) were then entered into multivariable analysis. Fully adjusted final models for hospitalization and severe disease included gender, age, education, health care workers (HCW), smoking, seasonal influenza vaccination in 2008–2009, delay in consultation, antiviral use before hospital admission, pregnancy, obesity, and sub-categories of underlying medical conditions. The fully adjusted final model for death included gender, age, education, delay in consultation, antiviral use before hospital admission, obesity and sub-categories of underlying medical conditions. Sensitivity analyses were performed by excluding missing data and by excluding HCW from the analysis.

Statistical analysis was performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). A two-sided P value of <0.05 was considered to indicate statistical significance.

Results

For the 1033 non-hospitalized patients, a phone number was unknown for 300 (29%) and 286 (28%) could not be reached despite at least five separate attempts (Figure 2). Among the 447 persons who were reached, 11 (2%) refused to participate, and one was excluded because of failure to speak English or French. The unreachable patients were comparable to those reached with regards to the proportion of men/women (44%/56% versus 47%/53%, respectively, $P = 0.37$) and to the age distribution (mean/median age 26.3/24 versus 27.2/22, Wilcoxon test, $P = 0.64$).

Among the 435 non-hospitalized patients who agreed to participate, 40 (9%) reported that they had been hospitalized ≥ 24 hours with their pH1N1 illness. These 40 patients were re-classified accordingly, giving a final sample of 395 non-hospitalized patients (Figure 2). An overall sample of 395 was considered proportional to the number of hospitalized cases and further attempts to reach non-hospitalized patients were stopped at this point.

For the 375 hospitalized cases, the phone number was unknown for 48 (13%) and 25 (7%) could not be reached (Figure 2). Among the 302 hospitalized cases that were reached, 4 (1%) refused to participate, one was excluded because of failure to speak English or French, and 16 (5%) were excluded because they declared reasons other than pH1N1 infection as the primary cause of hospitalization. Data on hospitalized patients were validated with the admitting hospital. The final sample was 321 hospitalized cases (including the 40 re-classified patients), of which 47 (15%) were admitted to an ICU and 15 (5%) died. All deaths occurred in hospital, and four of the deceased patients were not admitted to the ICU before death.

When comparing non-hospitalized and hospitalized cases in univariate analysis, factors significantly associated with hospitalization were as follows: age <5, 50–59, and ≥ 60 years (compared to age 5–19 years); lower education level; smoking; consulting a physician very early (the day of disease onset) or late (5 days or more after disease onset); having at least one underlying medical condition; and obesity (especially morbid obesity; Table 2). Health care workers represented 17% of non-hospitalized cases but only 2% of hospitalized patients. Antiviral therapy was taken by 22% of non-hospitalized cases and 17% of hospitalized cases before their hospital admission. Asthma was the underlying medical condition most frequently present in all types of cases and increased the risk of being hospitalized by 2.6-fold. The risk of hospitalization was highest (OR = 24.8) in patients with neuromuscular disorders. Hospitalized cases declared having anemia (mostly sickle cell anemia) more frequently than non-hospitalized patients (5% versus 0% for anemia; 4% versus 0% for sickle cell anemia, $P \leq 0.001$ for both comparisons).

In multivariable analysis, age <5 years (OR = 5.5), consultation ≥ 5 days after illness onset (OR = 1.9), and presence of ≥ 1 underlying chronic condition (OR = 4.9) were significantly associated with hospitalization (Table 2). All underlying chronic conditions, with the exception of immune-suppression, were significantly associated with hospitalization. Health care workers had lower risk of being hospitalized.

Among hospitalized patients, none of the examined factors further significantly increased the risk of admission to an ICU or death. Hospitalized patients who took antiviral medication before hospital admission had significant

Table 1. Participant characteristics by study group

Characteristics	Non-hospitalized, <i>n</i> = 395 <i>N</i> (%)	Hospitalized			
		All, <i>n</i> = 321 <i>N</i> (%)	Non-severe, <i>n</i> = 259 <i>N</i> (%)	Admitted to ICU, <i>n</i> = 47 <i>N</i> (%)	Deceased, <i>n</i> = 15 <i>N</i> (%)
Female gender	220 (56)	167 (52)	126 (49)	30 (64)	11 (73)
Age, years, mean (median)	27 (22)	29 (24)	28 (19)	31 (27)	52 (56)
<5	18 (5)	57 (18)	53 (20)	4 (9)	0 (0)
5–19	160 (41)	88 (27)	77 (30)	10 (21)	1 (7)
20–34	90 (23)	44 (14)	32 (12)	10 (21)	2 (13)
35–49	64 (16)	53 (17)	35 (14)	14 (30)	4 (27)
50–59	441 (11)	40 (12)	33 (13)	5 (11)	2 (13)
60+	19 (5)	39 (12)	29 (11)	4 (9)	6 (40)
Education* ^{***}					
high school not completed	49 (12)	61 (19)	47 (18)	10 (21)	4 (27)
High school/professional degree	108 (27)	85 (26)	70 (27)	14 (30)	1 (7)
College degree	92 (23)	64 (20)	50 (19)	10 (21)	4 (27)
University degree	123 (31)	62 (19)	55 (21)	4 (9)	3 (20)
Health care worker	68 (17)	8 (2)	4 (2)	4 (9)	0 (0)
Smoking**	44 (11)	48 (15)	37 (14)	9 (19)	2 (13)
Seasonal influenza vaccination in 2008–2009**	145 (37)	120 (37)	95 (37)	18 (38)	7 (47)
Consultation, days after symptoms onset; mean (median)**	3.6 (3)	3.6 (3)	3.7 (3)	3.2 (2)	4.8 (4)
0–1 days	96 (24)	82 (26)	65 (25)	14 (30)	3 (20)
2–4 days	211 (53)	123 (38)	100 (39)	18 (38)	5 (33)
5 days or more	82 (21)	85 (26)	65 (25)	13 (28)	7 (47)
Antiviral use before hospitalization**	85 (22)	54 (17)	48 (19)	4 (9)	2 (13)
Pregnancy	10 (3)	10 (3)	9 (3)	1 (2)	0 (0)
Underlying medical condition, at least one	76 (19)	186 (58)	128 (49)	29 (66)	9 (60)
Cardiac***	10 (3)	41 (13)	30 (12)	8 (17)	3 (20)
Diabetes mellitus	12 (3)	38 (12)	27 (10)	8 (17)	3 (20)
Renal†	4 (1)	18 (6)	15 (6)	3 (6)	0 (0)
Immune-suppression††	18 (5)	26 (8)	17 (7)	4 (9)	5 (33)
Asthma†††	35 (9)	64 (20)	54 (21)	8 (17)	2 (13)
Pulmonary‡	15 (4)	43 (13)	31 (12)	9 (19)	3 (20)
Neuromuscular‡‡	1 (0.3)	19 (6)	15 (6)	3 (6)	1 (7)
Other conditions	7 (2)	32 (10)	22 (8)	7 (15)	3 (20)
Anemia	0 (0)	16 (5)	10 (4)	6 (13)	0 (0)
Sickle cell anemia	0 (0)	12 (4)	9 (3)	3 (6)	0 (0)
Liver	0 (0)	5 (2)	4 (2)	1 (2)	0 (0)
Metabolic	1 (0)	4 (1)	4 (2)	0 (0)	0 (0)
Cancer	6 (2)	5 (2)	2 (1)	0 (0)	3 (20)
Obesity**, BMI ≥30†††	73 (18)	80 (25)	62 (24)	13 (28)	5 (33)
BMI ≥40 [§]	6 (3)	14 (8)	10 (7)	2 (6)	1 (7)

ICU, intensive care unit.

*For children <18 years, education of the mother.

**For these variables, missing values were present in 1–15%, with a maximum of 21% for obesity.

***Includes congestive heart failure, coronary artery disease, congenital heart disease, and valve replacement.

†Mostly chronic renal insufficiency.

††HIV/AIDS; chemo- and radiotherapy for cancer, long-term corticosteroid treatment.

†††Confirmed by a pulmonary function test or severe enough to have required hospitalization or systemic corticosteroids in the past 12 months.

‡Mostly chronic obstructive pulmonary disease and congenital pulmonary disorders in children.

‡‡Mostly cerebral palsy, muscular dystrophy, developmental delay.

‡‡‡In children defined according to Ref. 25.

§Defined only in adults ≥18 years.

Figure 2. Enrollment sheet.

reduction in the risk of severe disease [OR = 0.3; 95% confidence interval (CI): 0.1–0.8; $P = 0.015$] (Table 2). In a separate model for death among hospitalized cases (data not shown), the only significant association with death was observed for age ≥ 60 years (OR = 14.4, 95% CI: 1.0–197.3, $P = 0.046$) and immune suppression (OR = 7.3, 95% CI: 1.5–35.0, $P = 0.013$).

In sensitivity analyses either restricted to patients without missing data or excluding HCW, results were similar (data not shown).

Discussion

Our data indicate that young age group (<5 years), underlying chronic conditions and late consultation (5 days or more after symptom onset), was associated with increased risk of hospitalization for pH1N1, whereas age ≥ 60 years and immune suppression were associated with increased risk of death. As observed globally, age is an important risk factor for pH1N1 hospitalization. Our results show a relatively high proportion of children <5 years of age among hospitalized patients but a small proportion in this age category requiring ICU admission and no deaths. This suggests that physicians may be more inclined to admit young children for less severe disease. In contrast, patients aged ≥ 60 years were disproportionately represented among deaths despite their small number among non-hospitalized patients. This is consistent with other reports showing that the risk of death in patients with pH1N1 increased with advanced age: older individuals may have had a lower inci-

dence but if they became infected they were more likely to progress to severe illness.^{5,10,11,13,15,19}

Presence of underlying chronic conditions was the strongest and most consistent factor contributing to pH1N1 hospitalization, ICU admission, and death. The risk of hospitalization was similar for each specific chronic condition except for immune suppression and neurological disease. Immune suppression was not associated with hospitalization. However, once hospitalized, immune suppression was the only underlying condition associated with death. Neurological diseases as a group showed the strongest association with hospitalization when compared to non-hospitalized patients. Since 2005, both the National Advisory Committee on Immunization in Canada (NACI) and the Advisory Committee on Immunization Practice (ACIP) in the United States have recommended seasonal influenza vaccine for people with cognitive dysfunction, spinal cord injury, seizure disorder, neuromuscular disorders or any such conditions that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration.^{26,27} Such conditions may be of particular concern for pH1N1 given studies showing greater recognition of receptors in the lung and higher likelihood of primary viral pneumonia associated with that virus.^{28–30} In line with other reports, we found that a high proportion of patients admitted with pH1N1 had asthma.^{23,31} Other reports suggested that patients with pH1N1 illness are more likely to have asthma compared to seasonal influenza A¹² and compared to patients with influenza-like illness who tested negative for pH1N1.¹

Table 2. Odds ratios for hospitalization or ICU admission/death for various potential risk factors

Variables	Odds Ratio (95% confidence interval) for different comparisons			
	Hospitalized (321)/ Non-hospitalized (395)		ICU or death (62)/ Hospitalized non-severe (259)	
	Univariate	Multivariable*	Univariate	Multivariable*
Female gender	0.9 (0.6–1.2)	1.2 (0.7–1.9)	2.06 (1.2–3.7)	2.1 (0.9–5.1)
Age				
<5 years	5.8 (3.2–10.4)	5.5 (2.1–14.3)	0.5 (0.2–1.7)	0.5 (0.1–1.9)
5–19 years	Reference	Reference	Reference	Reference
20–34 years	0.9 (0.6–1.4)	2.6 (0.5–13.3)	2.6 (1.0–6.6)	2.1 (0.2–24.2)
35–49 years	1.5 (1.0–2.4)	4.5 (0.9–23.2)	3.6 (1.5–8.4)	1.7 (0.2–18.3)
50–59 years	1.7 (1.0–2.7)	4.3 (0.8–23.8)	1.5 (0.5–4.2)	0.6 (0.04–7.5)
60 years and older	3.7 (2.0–6.8)	2.2 (0.7–6.5)	2.4 (0.9–6.3)	1.1 (0.2–7.2)
Education				
High school not completed	2.5 (1.5–4.0)	1.3 (0.7–2.4)	2.3 (0.9–6.3)	1.5 (0.4–4.9)
Non-university certificate/diploma	1.5 (1.0–2.1)	1.2 (0.7–1.8)	1.9 (0.8–4.6)	1.4 (0.5–4.1)
University degree	Reference	Reference	Reference	Reference
Health care worker	0.1 (0.1–0.3)	0.2 (0.1–0.4)	2.8 (0.7–11.7)	4.3 (0.8–24.7)
Smoking	1.9 (1.2–2.9)	1.3 (0.7–2.2)	0.9 (0.4–2.0)	0.7 (0.3–1.7)
Seasonal influenza vaccination in 2008–2009	1.3 (0.9–1.8)	1.0 (0.6–1.5)	1.2 (0.6–2.1)	0.8 (0.4–1.8)
Consultation, days after symptom onset				
0–1 days	1.5 (1.0–2.1)	1.5 (0.9–2.4)	1.1 (0.6–2.3)	1.7 (0.7–3.9)
2–4 days	Reference	Reference	Reference	Reference
5 days or more	1.8 (1.2–2.6)	1.9 (1.2–2.9)	1.3 (0.7–2.6)	1.5 (0.7–3.4)
Antiviral use before hospitalization	0.9 (0.6–1.3)	1.0 (0.6–1.6)	0.4 (0.2–1.1)	0.3 (0.1–0.8)
Pregnancy (ref: no, female 14–49 years)	1.9 (0.8–4.9)	2.4 (0.8–7.3)	0.2 (0.02–1.7)	0.2 (0.02–1.8)
Underlying medical conditions				
At least one**	4.5 (3.2–6.3)	4.9 (3.2–7.3)	1.6 (0.9–2.9)	1.5 (0.8–2.9)
Cardiac	5.6 (2.8–11.4)	2.7 (1.1–6.5)	1.6 (0.8–3.5)	2.1 (0.8–6.1)
Diabetes	4.3 (2.2–8.4)	2.7 (1.1–6.5)	1.9 (0.9–4.0)	1.4 (0.5–3.8)
Pulmonary	3.9 (2.1–7.2)	2.5 (1.2–5.4)	1.8 (0.8–3.7)	1.7 (0.8–4.3)
Asthma	2.6 (1.6–4.0)	2.8 (1.6–4.7)	0.7 (0.3–1.5)	0.5 (0.3–1.3)
Immune-suppression	1.8 (0.99–3.4)	0.8 (0.4–1.9)	2.4 (1.0–5.7)	3.0 (0.9–9.7)
Neuromuscular	24.8 (3.3–185.7)	22.2 (2.6–186.0)	1.1 (0.4–3.5)	0.9 (0.2–3.6)
Renal	5.8 (1.9–17.3)	4.8 (1.3–17.7)	0.8 (0.2–3.0)	0.4 (0.08–2.0)
Other	6.1 (2.7–14.1)	5.6 (2.0–15.7)	2.1 (0.9–4.6)	1.2 (0.4–3.4)
Obesity (BMI ≥30)	2.2 (1.4–3.0)	1.3 (0.8–2.0)	1.1 (0.6–2.0)	1.0 (0.5–2.3)
BMI ≥40 (only in adults)***	3.1 (1.2–8.4)	2.0 (0.6–6.2)	0.9 (0.2–3.3)	0.4 (0.09–2.0)

BMI, body mass index; ICU, intensive care unit.

In bold, $P < 0.05$.*Adjusted for all variables listed in the table, excepting underlying condition, at least one; and BMI defined as ≥ 40 .

**For this variable, a separate model was constructed (multivariable adjusted for age, gender, obesity, being a health care worker, seasonal influenza vaccination, smoking, delay in consultation, antiviral use before admission, pregnancy, and education).

***For this variable, a separate model was constructed only in adults (multivariable adjusted for age, gender, underlying condition, being a health care worker, seasonal influenza vaccination, smoking, delay in consultation, antiviral use before admission, pregnancy, and education).

The point estimate for the association of at least one underlying medical condition with severe outcomes among hospitalized patients estimated in our study (OR = 1.5, 95% CI: 0.8–2.9) is similar to that reported in another study from Canada by Campbell *et al.*¹⁵ among patients admitted to hospital with pH1N1 across the 13 provinces and territories of Canada, including Quebec (OR = 1.5, 95% CI: 1.1–2.1). Campbell *et al.* relied upon enhanced

surveillance reporting by provinces and lacked information on underlying medical conditions and aboriginal status for two of the provinces (including the largest province of Ontario); conversely, we actively queried all participants on a standardized and detailed list of variables of interest, minimizing missing information. The larger CI and absence of statistical significance in our study may be explained by a lack of power because our sample size (62 severe

outcomes and 259 non-severe hospitalized) is smaller than that of Campbell *et al.* (308 severe and 1171 non-severe). Some differences in associations for severe outcomes with age groups and specific underlying conditions may also be explained by differences in populations (aboriginal status reported for 24% of the patients in Campbell's study, compared to <1% in our study), the more extensive list of adjustment variables we included, differences in the specific study period (April–July versus April–September for Campbell *et al.*), as well as differences in the propensity for testing and admitting patients.

While obesity and morbid obesity were associated with hospitalization in univariate analysis, their effect disappeared after adjustment for gender, age, smoking, education, and underlying medical conditions. Other conditions associated with obesity, such as hypertension, obstructive sleep apnea, or obesity-hypoventilation syndrome,¹⁰ not considered in our study, may also have contributed to this observation. Animal models suggest that obesity may play a specific and independent role in the pathogenesis of seasonal influenza through compromised T-cell-mediated immunity.^{32,33} Recently, advisory committees in Canada and the United States have added morbid obesity to influenza vaccine recommendations for the 2010–2011 season.^{34–36} Lower education and smoking were also initially found to be associated with hospitalization in univariate analysis in our study, but their effect disappeared in multivariable analysis. Ultimately, underlying medical conditions appear to be the most robust factor associated with hospitalization for pH1N1 illness. Such conditions are known to be more prevalent among the socially and economically disadvantaged segments of the population which we did not specifically assess.³⁷

The higher risk for hospitalization when seeking medical care late in the course of illness may be related to influenza complications such as advanced acute respiratory distress syndrome or bacterial superinfection. Bacterial superinfection was observed in 4–20% of patients hospitalized with pH1N1 infection, 13–29% of fatal pH1N1 cases,^{5,10,20} and 43% of fatal pH1N1 pediatric cases.⁴ At least one additional pathogenic respiratory virus or bacterium was found in nasopharyngeal aspirates of up to 76% of medically attended confirmed pH1N1 infection; however, only *Streptococcus pneumoniae* was associated with severe pH1N1 disease.³⁸ While we have not been able to assess antiviral therapy administered during the hospital stay, our results suggest that antiviral use before hospital admission may protect against severe pH1N1 outcomes and are consistent with data from other studies for seasonal^{39,40} and pH1N1 influenza.^{2,14,23,31}

The proportion of HCWs in the Quebec population is 3.6% compared to 17% observed among non-hospitalized patients enrolled in our study. This is unlikely to be

explained by a greater risk of pH1N1 among HCWs but more probably reflects the easier access to influenza testing for HCWs compared to the rest of the population. This latter hypothesis is supported by the 5-fold lower risk of hospitalization and severe disease for HCWs compared to non-HCW. The oversampling of HCW did not appear to influence our results because findings from multivariable analyses were robust with adjustment for HCW status and analyses excluding HCW showed similar estimates.

The findings we report are subject to several limitations. First, we reached the majority of hospitalized cases, but only 43% of non-hospitalized cases. We attained our enrollment target and few people contacted refused participation. Patients that were reached were comparable to those not reached on the basis of sex and age distribution, but it is possible that individuals who were not reached had other characteristics that differed. Second, we cannot exclude a role for recall bias: hospitalized cases may have better memory for events related to their hospitalization. Similarly, proxy responses provided by close relatives of deceased patients may differ from the rest of our study population. Social stigma may have led to underreporting of weight, smoking, or lower education. This is likely to apply equally to non-hospitalized and hospitalized cases which would then decrease the strength of associations found. Third, for non-hospitalized cases, testing for pH1N1 may have been subject to different health care-seeking behaviors by patients or different levels of clinical concern by physicians. In our analyses, we adjusted for being a HCW, as well as for education, smoking, and seasonal influenza vaccination which may be markers of health-seeking behavior. However, we cannot exclude the role of residual bias unaccounted for by our analyses. Physician vigilance may have led to persons with underlying conditions – hospitalized or non-hospitalized – being more often tested (and detected as pH1N1 positive) compared to those without underlying conditions. This would also have led to an underestimate of the effect of chronic conditions on the risk of hospitalization and disease severity. We identified age <5 years as a risk factor for hospitalization but sample size precluded further age stratification within that young age group. Infants and toddlers <24 months of age have been at recognized increased risk for hospitalization because of seasonal influenza for several years, but preschool children 2–5 years have not previously been identified at higher risk for hospitalization because of seasonal influenza, although they experience more medical visits.^{34,35} Thus, the more precise age-specific risk of pH1N1 hospitalization within this young age group warrants closer examination. Finally, while this study was well powered to assess the risk factors for hospitalizations, fewer participants admitted to ICU or dying were represented, limiting

the power to assess factors associated with those most severe outcomes.

In summary, we identified young age, underlying conditions and delayed consultation 5 days or more after illness onset as factors associated with higher risk of pH1N1 hospitalization. Older age (≥ 60 years) and immune suppression were associated with death among hospitalized patients. Antiviral medication taken before hospital admission did not protect against hospitalization but protected against subsequent more severe outcomes of ICU admission or death. Most variables associated with hospitalization and severe pH1N1 disease are also recognized risk factors for severe seasonal influenza. Further research is needed to better define whether obesity *per se* has an independent role in increasing the risk for severe pH1N1 illness.

Addendum

Substantial contribution to concept and design: R Gilca, G De Serres, N Boulianne, DM Skowronski; analysis: N Ouhoummane, É Fortin; interpretation of data: R Gilca, G De Serres, N Boulianne, N Ouhoummane, J Papenburg, M Douville-Fradet, É Fortin, M Dionne, G Boivin, DM Skowronski; critical writing: R Gilca, G De Serres, DM Skowronski; revising intellectual content R Gilca, G De Serres, N Boulianne, N Ouhoummane, J Papenburg, M Douville-Fradet, É Fortin, M Dionne, G Boivin, DM Skowronski.

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Conflicts of interest

Danuta M Sowronski was principal investigator of a trial for which influenza vaccine was provided free by Sanofi Pasteur. G Boivin has received research funding and speaking fees from Hoffman La Roche. M Dionne has received research funding from GSK. N Boulianne has received research funding from GSK and Sanofi Pasteur. Gaston De Serres has received research grants from GSK and Sanofi Pasteur for unrelated studies. M Douville-Fradet has acted as a paid consultant to Sanofi Pasteur once in 2008 and to Novartis, once in 2009. These consultations concerned all

types of vaccine and population needs, and the article does not concern what was discussed.

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