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See also related articles.

Context Between March and July 2009, the largest number of confirmed cases of 2009 influenza A(H1N1) infection occurred in North America.

Objective To describe characteristics, treatment, and outcomes of critically ill patients in Canada with 2009 influenza A(H1N1) infection.

Design, Setting, and Patients A prospective observational study of 168 critically ill patients with 2009 influenza A(H1N1) infection in 38 adult and pediatric intensive care units (ICUs) in Canada between April 16 and August 12, 2009.

Main Outcome Measures The primary outcome measures were 28-day and 90-day mortality. Secondary outcomes included frequency and duration of mechanical ventilation and duration of ICU stay.

Results Critical illness occurred in 215 patients with confirmed (n=162), probable (n=6), or suspected (n=47) community-acquired 2009 influenza A(H1N1) infection. Among the 168 patients with confirmed or probable 2009 influenza A(H1N1), the mean (SD) age was 32.3 (21.4) years; 113 were female (67.3%) and 50 were children (29.8%). Overall mortality among critically ill patients at 28 days was 14.3% (95% confidence interval, 9.5%-20.7%). There were 43 patients who were aboriginal Canadians (25.6%). The median time from symptom onset to hospital admission was 4 days (interquartile range [IQR], 2-7 days) and from hospitalization to ICU admission was 1 day (IQR, 0-2 days). Shock and nonpulmonary acute organ dysfunction was common (Sequential Organ Failure Assessment mean [SD] score of 6.8 [3.6] on day 1). Neuraminidase inhibitors were administered to 152 patients (90.5%). All patients were severely hypoxemic (mean [SD] ratio of PaO_2 to fraction of inspired oxygen [FIO_2] of 147 [128] mm Hg) at ICU admission. Mechanical ventilation was received by 136 patients (81.0%). The median duration of ventilation was 12 days (IQR, 6-20 days) and ICU stay was 12 days (IQR, 5-20 days). Lung rescue therapies included neuromuscular blockade (28% of patients), inhaled nitric oxide (13.7%), high-frequency oscillatory ventilation (11.9%), extracorporeal membrane oxygenation (4.2%), and prone positioning ventilation (3.0%). Overall mortality among critically ill patients at 90 days was 17.3% (95% confidence interval, 12.0%-24.0%; n=29).

Conclusion Critical illness due to 2009 influenza A(H1N1) in Canada occurred rapidly after hospital admission, often in young adults, and was associated with severe hypoxemia, multisystem organ failure, a requirement for prolonged mechanical ventilation, and the frequent use of rescue therapies.

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THE REEMERGENCE OF PANdemic influenza has been anticipated since the Hong Kong (H3N2) influenza pandemic of 1968. In recent years, there has been substantial concern that a pandemic would involve the novel H5N1 avian flu variant, which has demonstrated an ability to cause severe disease when transmitted to humans.[1,2] However, this spring the US Centers for Disease Control and Prevention reported the occurrence of a 2009 influenza A(H1N1) in 2 children in southern California.[3] Subsequently, infection with this virus has been reported in virtually every country.[4-7] The World Health Organization declared the first phase 6 global influenza pandemic of the century on June 11, 2009.[8]

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Table 1. Demographic Characteristics of Critically Ill Patients With Confirmed or Probable 2009 Influenza A(H1N1) Infection

	No. (%) of Patients (N = 168)[a]
Age, mean (SD), y	32.3 (21.4)
≥18 (adults)	118 (70.2)
<18 (children and adolescents)	50 (29.8)
Female sex	113 (67.3)
Health care worker	9 (5.4)
Influenza vaccination in 2008 or 2009	10 (6.0)
Test score, mean (SD)	
APACHE II (age ≥18 y)	19.7 (8.7)
PRISM III (age <18 y)	9.1 (9.8)
Nosocomial acquisition	16 (9.5)
Race	
White	67 (39.9)
First nations, Inuit, Métis, or aboriginal	43 (25.6)
Black	14 (8.3)
Other[b]	16 (9.5)
Unknown	28 (16.7)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; PRISM, Pediatric Risk of Mortality.
[a] Unless otherwise indicated.
[b] Indicates Asian (eg, Chinese, Japanese, Vietnamese, Cambodian, Indonesian, Laotian, Korean, Fillipino), South Asian (eg, East Indian, Pakistani, Sri Lankan, Punjab, Bangladeshi), Arab/West Asian (eg, Armenian, Egyptian, Iranian, Lebanese, Moroccan), or Latin American (eg, Mexican, Central/South American).

The largest numbers of confirmed cases have been documented in the United States, Mexico, Canada, Chile, and Australia.[9] Mexico and Canada have both experienced large localized outbreaks of infection with severe illness requiring intensive care unit (ICU) admission and ventilator support. This report describes the epidemiological characteristics, clinical features, treatments, and outcomes of a multicenter cohort of critically ill adult and pediatric Canadian patients.

METHODS

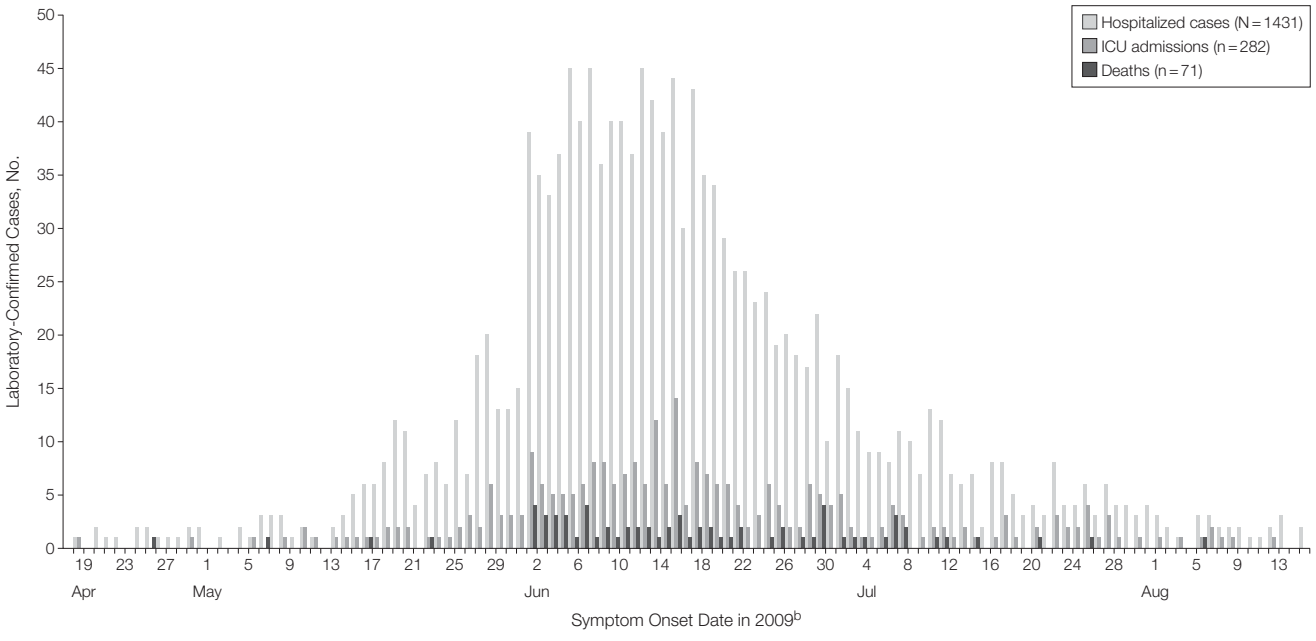
Study Design

In response to an outbreak of 2009 influenza A(H1N1) in Mexico, members of the Canadian Critical Care Trials Group (CCCTG) designed a multicenter observational study of critically ill patients infected with 2009 influenza A(H1N1) (eAppendix is available at http://www.jama.com). After several cycles of feedback and pilot testing, forms were widely disseminated to ICU physicians, and uploaded to the CCCTG and other critical care society Web sites on May 3, 2009.[10] Data were collected retrospectively or prospectively on all patients with 2009 influenza A(H1N1)–related critical illness admitted to the ICU between April 16 and August 12, 2009. Research ethics board approval was granted by Sunnybrook Health Sciences Centre as the central coordinating center on April 30, 2009, and by each participating local research ethics board. The need for a priori informed consent was waived because of the noninterventional study design.

Data Collection

Eligible patients included all adult and pediatric critically ill individuals admitted to participating hospitals in Canada with confirmed, probable, or suspected 2009 influenza A(H1N1) infection, according to case definitions developed by the World Health Organization and the Canadian National Microbiology Laboratory.[10,11] Critically ill patients were defined as (1) those admitted to a pediatric or adult ICU or those requiring mechanical ventilation (invasive or noninvasive), (2) those with a fraction of inspired oxygen

Figure 1. Patients With 2009 Influenza A(H1N1) Admitted to the Hospital, Intensive Care Unit (ICU), or Who Died in Several Canadian Provinces (n=116) and in the Greater Winnipeg Region, Manitoba, Canada (n=52) Between April 18, 2009, and August 15, 2009[a]



[a] Used with permission, Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada.
[b] May indicate specimen collection date.

(FIO_2) concentration greater than or equal to 60%, or (3) those with the need for intravenous infusion of inotropic or vasopressor medication. Suspected cases of 2009 influenza A(H1N1) in the presence of a strong epidemiologic link were initially included because confirmatory testing was unavailable in some hospitals when diagnostic laboratories were overwhelmed with testing requests once the pandemic was under way.

Eligibility criteria were confirmed and data were recorded by research coordinators or site investigators at each center (eAppendix). Severity of illness was assessed in adults and children using the Acute Physiology and Chronic Health Evaluation (APACHE) II and Pediatric Risk of Mortality (PRISM) III scores.[12,13] Comorbidities, including major comorbidities defined a priori, were recorded as the presence of 1 or more of the following chronic medical conditions: congestive heart failure; cerebrovascular, neoplastic, chronic liver or renal diseases; and use of immunosuppressant medications.[14]

The primary outcome measure was mortality at 28 days after the onset of critical illness as defined by the eligibility criteria. Secondary outcomes included frequency and duration of mechanical ventilation and duration of ICU and hospital stay. Data were submitted to the coordinating center and checked for errors by manual inspection and electronic range limits.

Analysis

Descriptive statistics included frequency analysis (percentages) for categorical variables and means and standard deviations or medians and interquartile ranges (IQRs) for continuous variables. To test for differences in baseline characteristics between those with confirmed or probable and those with suspected disease, and those who survived vs those who died, a 2-sample *t* test or the Wilcoxon rank sum test was used for continuous variables as appropriate and the χ^2 test or Fisher exact test was used for discrete variables. Daily variables are presented at days 1, 3, 7, and 14.

The Kaplan-Meier method in which patients discharged from the ICU alive were censored at 28 days was used to depict the probability of survival over the duration of follow-up and to generate survival curves. The discriminative ability of the day 1 APACHE II and SOFA scores on mortality were compared by testing the difference in C statistics (area under the receiver operating curve). The 95% confidence intervals (CIs) and *P* values were reported to reflect a 2-tailed α level of .05. The statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Characteristics of Study Patients and Hospitals

Between April 16 and July 13, 2009, 215 critically ill patients were admitted to 38 study ICUs (median of 16 ICU beds[15-34]; median hospital size, 463 beds [IQR, 238-524 beds]) with confirmed (n=162), probable (n=6), or suspected (n=47) 2009 influenza A(H1N1) infection. Patients having confirmed or probable 2009 influenza A(H1N1) infection were significantly younger, had a longer duration of mechanical ventilation and ICU stay, and higher mortality than those with suspected disease. Therefore, all analyses were restricted to the 168 patients with confirmed or probable 2009 influenza A(H1N1) infection (TABLE 1). The mean (SD) age was 32.3 (21.4) years; 113 patients were female (67.3%), 50 were children (29.8%), and there were 43 aboriginal Canadians (25.6%). There were 52 critically ill patients from the greater Winnipeg region, in the province of Manitoba, and 116 patients were from other provinces (FIGURE 1). Sixteen cases originated from nosocomial transmission; none of these were health care workers.

Among adults, the mean (SD) APACHE II score was 19.7 (8.7); and among pediatric patients, the mean (SD) PRISM III score was 9.1 (9.8). At presentation, comorbidities were present in 165 patients (98.2%) (TABLE 2). However, major comorbidities were present in only 51 patients (30.4%). The most common individual comorbidities were chronic lung disease (41.1%), obesity (33.3%), hypertension (24.4%), and ever smoking (22.6%). The mean (SD) body mass index (BMI; calculated as weight in kilograms divided by height in me-

Table 2. Comorbidities of Critically Ill Patients With Confirmed or Probable 2009 Influenza A(H1N1) Infection

	No. (%) of Patients (N = 168)[a]
No. of comorbidities, median (IQR)	2 (1-4)
Any comorbidity	165 (98.2)
Major comorbidity[b]	51 (30.4)
Chronic lung disease[c]	69 (41.1)
Asthma	38 (22.6)
COPD	16 (9.5)
Bronchopulmonary dyplasia	3 (1.8)
Other	31 (18.5)
Obesity[d]	56 (33.3)
Hypertension	41 (24.4)
Ever smoker	38 (22.6)
Type 1 or 2 diabetes	35 (20.8)
Immune suppression[c]	33 (19.6)
Corticosteroid use	26 (15.5)
Chemotherapy	6 (3.6)
HIV/AIDS	2 (1.2)
Other	14 (8.3)
Neurological disease[c]	26 (15.5)
Cerebrovascular disease	8 (4.8)
Seizures	13 (7.7)
Cerebral palsy	16 (9.5)
Other	6 (3.6)
Cardiac disease[c]	25 (14.9)
Ischemic heart	11 (6.5)
Congestive heart failure	12 (7.1)
Valvular heart	5 (3.0)
Congenital heart	5 (3.0)
Arrhythmia	6 (3.6)
Pregnancy	13 (7.7)
Gastrointestinal tract disease	11 (6.5)
Chronic renal insufficiency[e]	12 (7.1)
Substance abuse	10 (6.0)
Autoimmune disease	8 (4.8)
Malignancy	6 (3.6)
Hematologic	5 (3.0)
Metastatic solid cancer	1 (0.6)
Scoliosis	6 (3.6)
Peripheral vascular disease	5 (3.0)
Cirrhosis	1 (0.6)

Abbreviations: COPD chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IQR, interquartile range.
[a] Unless otherwise indicated.
[b] Indicates presence of congestive heart failure, cerebrovascular disease, chronic renal disease, liver disease, systemic malignancy, or immune suppression.[14]
[c] The total and percentage may not add up within this category due to a patient having more than 1 subcategory of illness.
[d] Defined as a body mass index greater than 30. Body mass index was calculated as weight in kilograms divided by height in meters squared.
[e] Four patients were receiving long-term dialysis treatment.

Table 3. Organ Dysfunction Over Time Among 168 Critically Ill Patients

	Day 1 (N = 168)	Day 3 (n = 156)	Day 7 (n = 125)	Day 14 (n = 82)
SOFA score, mean (SD)[a]	6.8 (3.6)	6.6 (4.2)	6.1 (4.3)	5.7 (4.2)
Ratio of Pa_{O_2} to F_{IO_2}, mean (SD), mm Hg	147 (128)	168 (86)	172 (101)	190 (122)
Lowest SBP, mean (SD), mm Hg	95 (24)	104 (28)	107 (27)	112 (27)
Inotropes or vasopressors, No. (%)	55 (32.7)	58 (37.2)	31 (24.8)	14 (17.1)
Heart rate, mean (SD), /min	119 (28)	106 (26)	106 (29)	106 (25)
Creatinine, median (IQR), mg/dL	0.73 (0.50-1.15)	0.74 (0.52-1.19)	0.74 (0.55-1.28)	0.80 (0.57-1.72)
Platelet count, mean (SD), $\times 10^3/\mu L$	189 (87)	187 (93)	283 (171)	404 (228)
Bilirubin, median (IQR), mg/dL	0.41 (0.23-0.79)	0.44 (0.23-1.05)	0.50 (0.29-1.02)	0.47 (0.36-0.94)
White blood cell count, mean (SD), $\times 10^9/L$	9.4 (10.0)	9.1 (7.0)	11.3 (5.3)	13.4 (7.4)
AST, median (IQR), U/L	64 (37-126)	70.5 (42-163)	49 (31-96)	43 (29-65)
ALT, median (IQR), U/L	35 (21-68)	35 (25-69)	44.5 (24-74)	30 (20-61)
Creatine kinase, median (IQR), U/L	243 (99-922)	580 (203-1728)	228 (76-1046)	48 (22-91)
INR, mean (SD)	1.22 (0.27)	1.18 (0.29)	1.18 (0.27)	1.18 (0.18)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; F_{IO_2}, fraction of inspired oxygen; INR, international normalized ratio; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; SBP, systolic blood pressure.
SI conversion factors: To convert ALT to µkat/L, multiply by 0.0167; AST to µkat/L, multiply by 0.0167; bilirubin to µmol/L, multiply by 17.104; creatinine to µmol/L, multiply by 88.4; creatine kinase to µkat/L, multiply by 0.0167.
[a] Indicates sum of scores (range, 0-4) for each of 6 organ systems, in which a higher value reflects greater dysfunction.

Table 4. Clinical Course and Outcomes of Patients With Confirmed or Probable 2009 Influenza A(H1N1) Infection[a]

	No. (%) of Patients [95% CI] (N = 168)[b]
Time from ICU admission to death	
Day 14	18 (10.7) [6.6-16.6]
Day 28	24 (14.3) [9.5-20.7]
Day 90	29 (17.3) [12.0-24.0]
Time course of illness, d	Median (IQR)
Symptoms to hospital admission	4 (2-7)
Hospitalization to ICU admission	1 (0-2)
Hospitalization to death	14 (6-20)
	Median (IQR) [95% CI]
ICU length of stay, d	
Survivors	12 (5-22) [9-14]
Nonsurvivors	10 (4-19) [5-14]
Duration of ventilation, d	
Survivors	12 (6-20) [9-14]
Nonsurvivors	12 (4-20) [5-15]

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range.
[a] Data are to August 10, 2009; 5 additional patients died between days 28 and 90 after the onset of critical illness.
[b] Unless otherwise indicated.

ters squared) was 34.6 (11.0) and 28 patients (23.7%) were morbidly obese (BMI >40). The most common presenting symptoms were fever (90.5%), respiratory symptoms (94.6%), weakness (55.9%), and myalgias (40.1%). Concomitant presenting conditions included possible bacterial pneumonia (54 cases; 32.1%), hypotension requiring vasopressors (23 cases; 13.7%), asthma or chronic obstructive pulmonary disease exacerbation (23 cases; 13.7%), altered level of consciousness (17 cases; 10.1%), acute kidney injury (12 cases; 7.1%), and ischemic chest pain (5 cases; 3.0%).

Course of Illness and Treatments Received

The median time from symptom onset to hospital admission was 4 days (IQR, 2-7 days)[2-7] and from hospitalization to ICU admission was 1 day (IQR, 0-2 days) after presentation to the hospital. Only 10 patients (6%) had received a seasonal influenza vaccination in either of the past 2 years. Most patients (70.8%) had bilateral chest radiograph infiltrates (41.1% with 4-quadrant involvement) and 72.6% had acute lung injury at the onset of critical illness.

Of all patients, 136 (81.0%) were mechanically ventilated on the first day of ICU admission; 128 (76.2%) invasively and 55 (32.7%) noninvasively. Forty-seven patients (85.4%) who received noninvasive ventilation ultimately required invasive ventilation. The mean (SD) day 1 ratio of Pa_{O_2} to F_{IO_2} was 147 (128) mm Hg (TABLE 3); the mean (SD) day 1 F_{IO_2} value was 74% (26%) and the mean (SD) day 1 positive end-expiratory pressure (PEEP) was 9.8 (4.0) cm H_2O (eTable is available at http://www.jama.com).

The mean daily PEEP was greater than 10 cm H_2O for the first 2 weeks of mechanical ventilation. Over the first 2 weeks of critical illness, tidal volumes ranged from 8 to 9.1 mL/kg of ideal body weight; and carbon dioxide elimination was not substantially impaired. Barotrauma occurred in 14 patients (8.3%). Therapies for oxygenation failure included neuromuscular blockade (47 patients; 28.0%), inhaled nitric oxide (23 patients; 13.7%), high-frequency oscillatory ventilation (20 patients; 11.9%), extracorporeal membrane oxygenation (7 patients; 4.2%), and prone positioning ventilation (5 patients; 3.0%) (eTable).

Inotropes or vasopressors were used in 55 patients (32.7%) on day 1 after the onset of critical illness (Table 3), often with high levels of sedatives to facilitate patient-ventilator synchrony. Drug treatments included neuraminidase inhibitors (152 patients [90.5%] for a median of 5 days[4-8]), antibiotics (166 patients; 98.8%), and corticosteroids (85 patients; 50.6%).

Creatine kinase was moderately elevated over the first week of critical illness (median level, 580 U/L [IQR, 203-1728 U/L] by day 3; to convert creatine kinase to µkat/L, multiply by 0.0167) (Table 3). The mean leukocyte count was normal at admission and remained in the normal range for the first week. Clinical evidence of secondary bacterial pneumonia following ICU admission was found in 41 cases (24.4% of all patients) including 18 cases caused by *Staphylococcus aureus* and 5 cases caused by *Streptococcus pneumoniae*.

Outcomes

Among 168 critically ill patients with 2009 influenza A(H1N1) infection, 29 died (17.3%; 95% CI, 12.0%-24.0%). Eighteen patients died (10.7%; 95% CI, 6.6%-16.6%) within the first 14 days and 24 died (14.3%; 95% CI, 9.5%-20.7%) within 28 days from the onset of critical illness (TABLE 4 and FIGURE 2). Twenty-

one of those who died were female (72.4%) and 8 were male (27.6%). Of 50 children, only 4 died (8.0%). Of 9 health care workers, 5 required mechanical ventilation and none died. The median length of ICU stay was 12 days (IQR, 5-20 days)[5-20]; 12 days for survivors[5-22] and 10 days for nonsurvivors.[4-19] The median duration of ventilation was 12 days (IQR, 6-20 days) for both survivors[6-20] and nonsurvivors.[4-20] One patient died on a medical ward, while all others died in the ICU.

The primary reported causes of death included severe acute respiratory distress syndrome and hypoxemia, or complications thereof[5]; secondary infection and sepsis[6]; multiorgan dysfunction syndrome,[2] malignancy,[2] chronic obstructive pulmonary disease,[1] primary cardiac arrest[1]; tension pneumothorax,[1] cerebral edema[1]; and undetermined etiologies. Pulmonary embolism was believed to be contributory but not causal in 1 death.

Comparison of Survivors With Nonsurvivors

Patients who died were more likely to have higher severity of illness at presentation and greater organ dysfunction (TABLE 5). Although this overall population was young, older patients were more likely to die. There were no statistically significant differences in female sex distribution or aboriginal vs nonaboriginal status. The APACHE II and day 1 SOFA scores were significantly associated with overall mortality ($P<.001$ and $P=.002$, respectively) and there was no difference between the predictive value of these 2 scores (C statistics: 0.757 and 0.688, respectively; $P=.13$). Because nearly all patients received early treatment with neuraminidase inhibitors, we were unable to investigate differences in outcome due to treatment or timing of these agents (FIGURE 3).

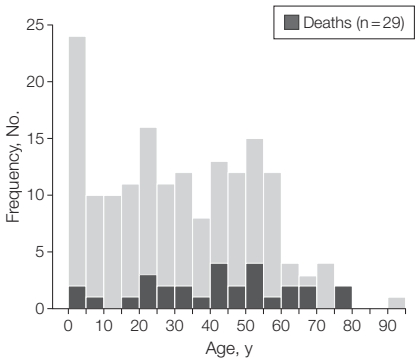
Comparison of All Patients

As of August 22, 2009, in the general Canadian population, among 7107 reported cases, 1441 required hospitalization (20.3%), 278 were admitted to the ICU (3.9%) (the 215 admitted by July 13, 2009, are reported in this series).[15] In comparing characteristics of all patients infected with 2009 influenza A(H1N1) infection, patients hospitalized, those admitted to the ICU, and those who died, the median age of patients was progressively greater along this continuum and there was a progressively greater proportion of patients with at least 1 underlying medical condition. The proportion of females was greater among those admitted to the ICU and among those who died compared with those infected and those admitted to hospital. There were a greater proportion of pregnant women requiring admission to the hospital and who died compared with the proportion among all of those infected.[15]

COMMENT

The spring outbreak of 2009 influenza A(H1N1) infection in Canada affected primarily young, female, and aboriginal patients without major comorbidities, and conferred a 28-day mortality of 14.3% among critically ill patients. A history of lung disease or smoking, obesity, hypertension, and

Figure 2. Age Distribution of 168 Critically Ill Patients With Confirmed or Probable 2009 Influenza A(H1N1)



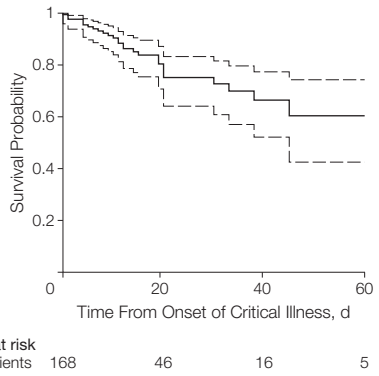
Intervals on the x-axis are equal to the lower limit and less than the upper limit of that age category.

Table 5. Comparison of Survivors and Nonsurvivors

	Survivors (n = 139)	Nonsurvivors (n = 29)	*P* Value
Age, mean (SD), y	30 (21)	42 (21)	.007
Female sex, No. (%)	92 (66)	21 (72)	.52
Comorbidities			
Ever smoker, No. (%)	32 (23)	6 (21)	.96
BMI, median (IQR)[a]	29 (24-39)	31 (28-41)	.33
Time course of illness, median (IQR), d			
Symptoms to hospital admission	4 (2-7)	5 (3-7)	.21
Hospitalization to ICU admission	0 (0-2)	1 (0-3)	.29
Characteristics at ICU admission			
APACHE II score, mean (SD)	18 (8)	26 (8)	<.001
Ratio of Pao_2 to Fio_2, median (IQR), mm Hg	124 (80-181)	85 (67-166)	.10
Initial mean arterial pressure, median (IQR), mm Hg	65 (58-77)	68 (58-83)	.31
Ventilation at ICU admission, mean (SD)			
Tidal volume for ideal body weight, mL/kg	9.2 (2.4)	8.6 (2.7)	.36
Plateau pressure, cm H_2O	25.6 (9.3)	28.0 (10.6)	.70
Set PEEP, cm H_2O	9.6 (3.8)	10.5 (4.7)	.36
Organ dysfunction, median (IQR)[b]			
SOFA score on day 1, mean (SD)	6.4 (3.4)	8.4 (3.5)	.01
Creatinine, mg/dL	0.71 (0.46-1.01)	0.97 (0.58-2.33)	.005
AST, U/L	60 (37-125)	71.5 (40-207)	.58
White blood cell count, $\times 10^9$/L	6.7 (3.8-12.1)	6.9 (3.7-9.5)	.63
Platelet count, mean (SD), $\times 10^3$/μL	195 (88)	161 (77)	.05
Bilirubin, mg/dL	0.41 (0.23-0.76)	0.52 (0.29-0.93)	.39
Creatine kinase, U/L	255 (104-1117)	221 (42-455)	.45

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; BMI, body mass index; Fio_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; PEEP, positive end expiratory pressure; SOFA, Sequential Organ Failure Assessment.
SI conversion factors: To convert AST to μkat/L, multiply by 0.0167; bilirubin to μmol/L, multiply by 17.104; creatinine to μmol/L, multiply by 88.4; creatine kinase to μkat/L, multiply by 0.0167.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Unless otherwise indicated.

Figure 3. Survival Curves of Critically Ill Patients With 2009 Influenza A(H1N1)



Dashed lines represent 95% confidence intervals. One patient died beyond day 60.

diabetes were the most common comorbidities. Critical illness occurred rapidly after hospital admission and was associated with severe oxygenation failure, a requirement for prolonged mechanical ventilation, and the frequent use of rescue therapies.

We identified unusual features of severe disease in the current pandemic compared with most previous well-characterized pandemics, including the (probable) H2N2 1890 Russian influenza pandemic, the H2N2 1957 Asian influenza pandemic, and the H3N2 1968 Hong Kong pandemic.[16-18] In these previous influenza pandemics, an increased predilection for infection among children and young adults has been documented,[9,19] although mortality curves were U shaped with increased deaths in the very young and the aged.

Our data suggest that severe disease and mortality in the current outbreak is concentrated in relatively healthy adolescents and adults between the ages of 10 and 60 years, a pattern reminiscent of the W-shaped curve previously seen only during the 1918 H1N1 Spanish pandemic.[20-22] Few patients older than 60 years in this study were admitted to the ICU (Figure 1). A potential biological basis for this observation is that patients in this age group have a cross-reactive antibody to 2009 influenza A(H1N1) at much higher rates than younger patients.[23]

The increased fraction of the aboriginal community presenting with severe 2009 influenza A(H1N1) infection is notable but not unique. This finding is reflected in the history of the 1918 H1N1 Spanish influenza pandemic during which mortality in aboriginal communities in North America (3%-9%) was many times higher than nonaboriginal communities (generally <0.75%).[24-29] In 1918, mortality within Alaskan and Labrador Inuit populations was 30% to 90%.[24,28,29] Although mortality was not substantially greater among aboriginal Canadians in this report, the number of patients with severe disease and knowledge of prior illness patterns in this community is cause for concern.

The tendency of females to develop severe 2009 influenza A(H1N1) infection in this series is striking. A general female susceptibility has not been observed in other influenza case series of variable severity including the initial reports of 2009 influenza A(H1N1) infections.[30,31] In most infectious diseases and related conditions such as sepsis and septic shock, males represent a larger proportion of cases and have a higher mortality.[32,33] The explanation for increased risk of severe disease and death among females in this report is unclear but the role of pregnancy as a risk factor has been noted in previous influenza pandemics.[34,35]

The most common comorbidities among critically ill patients in our study were lung disease, obesity, hypertension, and a history of smoking or diabetes, each occurring in 30% to 40% of patients. All these conditions are known to be increased in frequency in the aboriginal population that comprises a substantial portion of cases within this cohort.[36] The extent to which these comorbidities contribute to severity of disease is unclear because a large portion of the aboriginal population (which may be a risk factor itself on the basis of genetic susceptibility) often have such comorbidities.

Among critically ill patients, obesity has been shown to be a risk factor for increased morbidity, but not consistently with mortality.[37,38] The association of obesity with severe 2009 influenza A(H1N1) infection has been reported by others[39] and may be a novel finding of this pandemic; however, even though obesity was more common in our series than in the general Canadian population (33% vs approximately 24%), we did not find a significant difference in BMI between survivors and nonsurvivors.[40]

Critically ill patients with diabetes and hyperglycemia also are known to be at increased risk of complications and death; similarly, alcohol abuse, which is known to be a risk factor for acute respiratory distress syndrome, may have been a risk factor some patients in our series.[41] These relationships also have been reported with seasonal influenza.[42] The relative absence of serious comorbidities emphasizes that young, relatively healthy adults were the primary population affected by severe 2009 influenza A(H1N1) infection during this outbreak.

Patients with 2009 influenza A(H1N1) infection–related critical illness experienced symptoms for an average of 4 days prior to hospital presentation, but rapidly worsened and required care in the ICU within 1 to 2 days. Apart from the usual symptoms seen in seasonal influenza, these cases stand out for the presence of gastrointestinal tract symptoms, dyspnea, purulent sputum production, and occasional frothy lung fluid on cough or endotracheal aspiration. Chest radiographs demonstrating bilateral mixed interstitial or alveolar infiltrates were found in three-quarters of the patients.

Approximately one-third of patients required vasopressor support on day 1 following ICU admission; however, in many cases this appeared temporally associated with the need for substantial sedation to optimize ventilation. Broad-spectrum antibacterial agents were initiated in almost all patients because of the initial suspicion of community-acquired bacterial pneumonia. However, actual bacterial lung infection was typically documented later in the course of critical illness.

In addition, approximately one-third of patients in our cohort required advanced ventilatory support and rescue therapies for profound hypoxemic respiratory failure, including high levels of inspired oxygen and PEEP, pressure control, and airway pressure release ventilation, high-frequency oscillatory ventilation, prone positioning ventilation, neuromuscular blockade, inhaled nitric oxide, and extracorporeal membrane oxygenation. The fact that severe illness arises in a young, previously healthy population with a high probability of survival given the availability of appropriate resources has important societal implications.

In Winnipeg, Manitoba, Canada, site of the largest pandemic cohort of patients, the capacity for the care of critically ill patients was seriously challenged at the outbreak peak in June (Figure 1) with full occupancy of all regional ICU beds, similar to the 2002 Toronto, Ontario, Canada, experience with severe acute respiratory syndrome.[43] If, as expected, the prevalence of 2009 influenza A(H1N1) infection increases with the upcoming flu season, there will be an acutely increased demand for ICU care, including the need for rescue therapies that are not currently widely available.[44-46] Clinicians and policy makers will need to examine feasible methods to optimally expand and deploy ICU resources to meet this need.

This study has a number of strengths. It represents the largest series of patients with severe 2009 influenza A(H1N1) infection yet described, and includes both adults and children from geographically and racially diverse settings across Canada, which improves the generalizability of our results to other regions. These observations of the epidemiological risk factors, typical clinical features, response to therapy, and prognosis should aid in the recognition, diagnosis, and clinical management of such infections. Our finding that patients can often be supported through 2009 influenza A(H1N1) infection–related critical illness with prolonged, aggressive life support, and the expectation that the number of cases will likely increase substantially over the next 6 months, highlight important potential limitations in critical care capacity.

This study also has limitations. Our focus on severe disease requiring ICU admission may not reflect important presenting features in less severe cases. The ongoing deaths throughout the course of the study period suggest the possibility of late deaths after the observation period. This may result in a final hospital mortality rate that exceeds the mortality rate we are reporting. Although we describe cases in most regions of Canada, many were from an outbreak in a single province (Manitoba) and involved an aboriginal Canadian population near Winnipeg, which is Manitoba's largest city. This may lead to overrepresentation or underrepresentation of certain comorbidities and clinical features.

In conclusion, we have demonstrated that 2009 influenza A(H1N1) infection–related critical illness predominantly affects young patients with few major comorbidities and is associated with severe hypoxemic respiratory failure, often requiring prolonged mechanical ventilation and rescue therapies. With such therapy, we found that most patients can be supported through their critical illness.

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