Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection

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Abstract

Background: In the context of 2009 pandemic influenza (H1N1) virus infection (pandemic H1N1 influenza), identifying correlates of the severity of disease is critical to guiding the implementation of antiviral strategies, prioritization of vaccination efforts and planning of health infrastructure. The objective of this study was to identify factors correlated with severity of disease in confirmed cases of pandemic H1N1 influenza.

Methods: This cumulative case–control study included all laboratory-confirmed cases of pandemic H1N1 influenza among residents of the province of Manitoba, Canada, for whom the final location of treatment was known. Severe cases were defined by admission to a provincial intensive care unit (ICU). Factors associated with severe disease necessitating admission to the ICU were determined by comparing ICU cases with two control groups: patients who were admitted to hospital but not to an ICU and those who remained in the community.

Results: As of Sept. 5, 2009, there had been 795 confirmed cases of pandemic H1N1 influenza in Manitoba for which the final treatment location could be determined. The mean age of individuals with laboratory-confirmed infection was 25.3 (standard deviation 18.8) years. More than half of the patients (417 or 52%) were female, and 215 (37%) of 588 confirmed infections for which ethnicity was known occurred in First Nations residents. The proportion of First Nations residents increased with increasing severity of disease (116 [28%] of 410 community cases, 74 [54%] of 136 admitted to hospital and 25 [60%] of 42 admitted to an ICU; $p < 0.001$), as did the presence of an underlying comorbidity (201 [35%] of 569 community cases, 103 [57%] of 181 admitted to hospital and 34 [76%] of 45 admitted to an ICU; $p < 0.001$). The median interval from onset of symptoms to initiation of antiviral therapy was 2 days (interquartile range, IQR 1–3) for community cases, 4 days (IQR 2–6) for patients admitted to hospital and 6 days (IQR 4–9) for those admitted to an ICU ($p < 0.001$). In a multivariable logistic model, the interval from onset of symptoms to initiation of antiviral therapy (odds ratio [OR] 8.24, 95% confidence interval [CI] 2.82–24.1), First Nations ethnicity (OR 6.52, 95% CI 2.04–20.8) and presence of an underlying comorbidity (OR 3.19, 95% CI 1.07–9.52) were associated with increased odds of admission to the ICU (i.e., severe disease) relative to community cases. In an analysis of ICU cases compared with patients admitted to hospital, First Nations ethnicity (OR 3.23, 95% CI 1.04–10.1) was associated with increased severity of disease.

Interpretation: Severe pandemic H1N1 influenza necessitating admission to the ICU was associated with a longer interval from onset of symptoms to treatment with antiviral therapy and with the presence of an underlying comorbidity. First Nations ethnicity appeared to be an independent determinant of severe infection. Despite these associations, the cause and outcomes of pandemic HINI influenza may involve many complex and interrelated factors, all of which require further research and analysis.

In April 2009, Canada's first wave of pandemic influenza (H1N1) virus infections (pandemic H1N1 influenza) began. The highest burden of severe illness in Canada occurred in the province of Manitoba, where 45 Manitobans and 9 out-of-province patients were admitted to an intensive care unit (ICU). In this first wave, ICU staff and equipment were mobilized to expand bed capacity and ventilator capabilities to accommodate clinical need.

Although many individuals presented with mild, self-limited symptoms and no sign of pulmonary involvement, some people required admission to an ICU and received maximal life support measures.[1–3] Predicting disease and mitigating hazard in at-risk populations is an important aim of public heath epidemiology, and in preparation for future waves of pandemic H1N1 influenza, determining correlates of the severity of disease may be very important. Initial reports have suggested that, in addition to many of the previously known risk factors for complica-

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tions of seasonal influenza, obesity[4] and other underlying comorbidities[3,5] may be risk factors for severe disease. The interval from onset of symptoms to initiation of antiviral therapy or other treatment and supportive care was also associated with adverse outcome in a recent case series.[6] In a Canadian study of severe pandemic H1N1 influenza, First Nations people were proportionally overrepresented among patients in the ICU.[2] However, it is unclear if this association was independent of potential confounding factors. The ability to determine correlates of severe pandemic H1N1 disease and subsequent need for ICU resources in at-risk populations would provide opportunities for public and population health analysis and action, public education, strategic prioritization of vaccination efforts, efficient and equitable allocation and use of antiviral drugs, and development of infrastructure within the health system.

The objectives of this study were to identify factors that were correlated with severity of disease in confirmed cases of pandemic H1N1 influenza. Our hypothesis, which was based on existing literature, was that obesity, First Nations ethnicity and longer interval from onset of symptoms to treatment would be important determinants of the severity of disease.

Methods

Study design, population and variables

We designed this investigation as a cumulative case–control study. The study population consisted of all laboratory-confirmed cases of pandemic H1N1 influenza involving residents of the province of Manitoba for whom the final location of treatment was known: community, hospital or ICU. Infections were confirmed by reverse transcription polymerase chain reaction at the Cadham Provincial Laboratory in Winnipeg, Manitoba. We based our definitions of case severity on the type of care required. Severe cases were those in which the patient was admitted to an ICU within the province of Manitoba. We defined two control groups. Moderate cases were those in which the patient required admission to hospital but not to the ICU. Mild cases, also termed community cases, were those without admission to hospital.

We defined self-reported ethnicity as either First Nations or another ethnic group. First Nations peoples are one of the three officially recognized groups of Canadian Aboriginal peoples, the others being the Inuit and the Metis. We assessed income according to income quintiles based on each individual's location of residence, as defined by the postal code in the person's mailing address.[7] We combined the top three quintiles for comparison with the bottom two quintiles combined.

We defined the variable "any comorbidity" as referring to heart disease, diabetes mellitus, tuberculosis, asthma, smoking, neuromuscular disease, kidney disease, malignancy, immune suppression, lung disease, cognitive dysfunction, pregnancy, alcoholism, substance abuse and injection drug use.

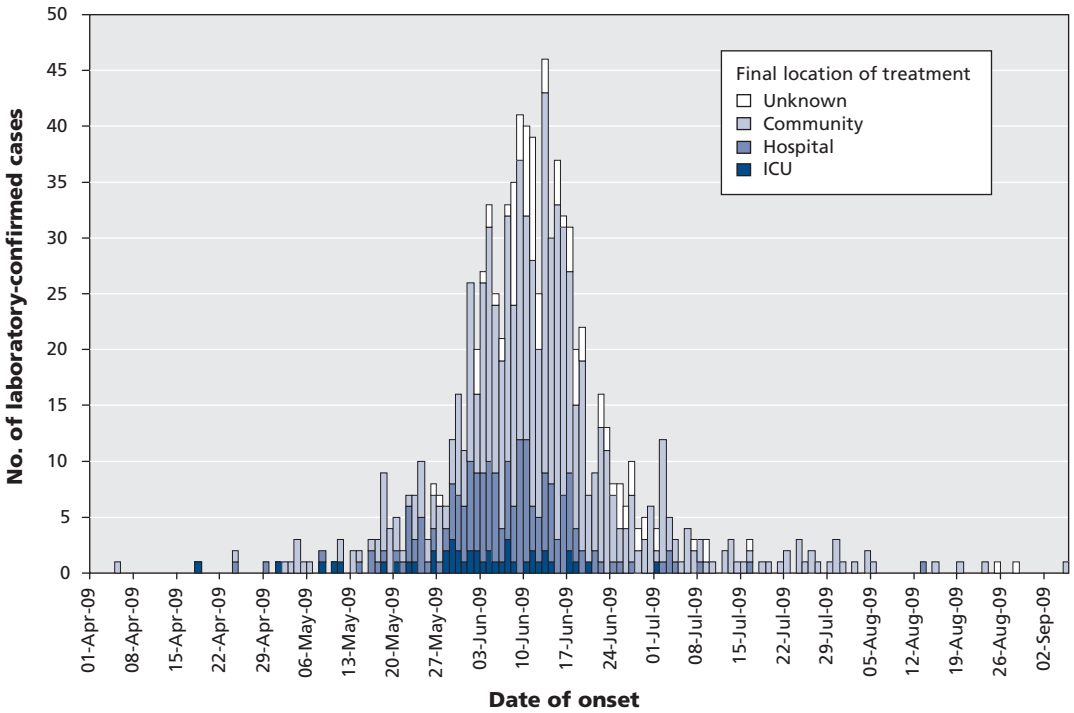

Figure 1: Epidemic curve of laboratory-confirmed cases of 2009 pandemic influenza (H1N1) virus infection in Manitoba according to final location of treatment (n = 889). The epidemic curve represents the dates of onset for confirmed cases, based on the earliest of the following dates: date of onset of symptoms, date of admission to hospital, date on which investigation form was received, date on which specimen was obtained or date on which report was received. For five additional cases, the date of onset according to this definition occurred before Apr. 2, 2009, and these cases are not represented in the figure. ICU = intensive care unit.

Data sources

In response to the emerging H1N1 pandemic, epidemiologists and clinician investigators from Manitoba Health and the University of Manitoba's Section of Critical Care independently created case report forms to facilitate disease surveillance and data collection regarding this novel infection. Public health nurses completed the provincial forms via interview, in person or by telephone, or by chart review for all confirmed cases of pandemic H1N1 influenza in the province of Manitoba. The information collected included patients' demographic characteristics, medical history, clinical information, treatments and outcome. The database of information collected by the University of Manitoba's Section of Critical Care contained prospectively collected data for all cases of pandemic H1N1 influenza in which the patient was admitted to an ICU in the province of Manitoba. Trained research nurses and medical students collected data about these patients. As a result of efficient data-sharing processes put in place by the province of Manitoba at the start of the pandemic H1N1 influenza outbreak, we were able to combine data elements from the two sources to create one complete record for each laboratory-confirmed case of pandemic H1N1 influenza. This study was approved by the Research Ethics Board at the University of Manitoba.

Analysis

We generated the following descriptive statistics: frequency analysis (percentages) for categorical variables and means (and standard deviations [SDs]) or medians (and interquartile ranges [IQRs]) for continuous variables. We assessed overall differences between groups in terms of severity of disease for continuous and categorical variables using analysis of variance (ANOVA) or the χ^2 test or Fisher's exact test, as appropriate. We used univariable and multivariable logistic regression to examine the relation between variables of interest and severity of disease. In particular, we compared cases of severe disease (i.e., those with ICU admission) with controls who remained in the community or who were admitted to hospital but not to the ICU. To assess the consistency of effect, we also compared community cases with cases involving admission to hospital but not the ICU. We express results from logistic regression analyses as odds ratios (ORs) and 95% confidence intervals (CIs), with ORs greater than 1.0 signifying greater risk of severe disease compared with the referent group. We estimated model parameters using the method of maximum likelihood. The confidence intervals and p values reported here reflect a two-tailed α level of 0.05.

Results

From the start of the epidemic (about Apr. 2) to Sept. 5, 2009, a total of 894 cases of pandemic H1N1 influenza were confirmed among Manitoba residents (Figure 1). The location of care could be determined for 795 (89%) of the confirmed cases: 569 (72%) of the patients remained in the community, 181 (23%) were admitted to a hospital but not the ICU, and 45 (6%) were admitted to an ICU. The mean age of infected individuals included in the analysis was 25.3 years (SD 18.8). The age-specific distribution of confirmed infections by location of care is illustrated in Figure 2. Females accounted for 417 (52%) of the infections. Ethnicity was known for 588 (74%) of the 795 infections; of these, First Nations individuals accounted for 215 (37%) of the confirmed infections. Health care workers accounted for 62 (8%) of all infections.

The mean age of infected individuals was 25.3 (SD 17.5) for community cases, 23.0 (SD 21.9) for patients who were admitted to hospital but not the ICU and 33.4 (SD 19.7) for those admitted to the ICU ($p = 0.004$) (Table 1). First Nations residents accounted for 116 (28%) of 410 community cases, 74 (54%) of 136 patients admitted to hospital and 25 (60%) of 42 admitted to the ICU ($p < 0.001$). Females represented 296 (52%) of the 569 community cases and 90 (50%) of the 181 hospital admissions without ICU care, but 31 (69%) of the 45 ICU cases ($p = 0.03$). Of the 34 adult patients admitted to the ICU with comorbidities, the proportion with clinical obesity, defined as body mass index greater than 30, was 62% (n = 21). Height and weight were not recorded consistently enough for patients in the two control groups to allow analysis of the relation between obesity and severe outcomes. The presence of an underlying medical condition, including pregnancy, increased with severity of disease (201 [35%] of the 569 community cases, 103 [57%] of the 181 patients admitted to hospital and 34 [76%] of the 45 patients admitted to the ICU; $p < 0.001$). The proportions of female patients with confirmed pandemic H1N1 influenza who were pregnant was 3% (9 of 296 female patients) in the community group, 20% (18 of 90 female patients) in the hospital group and 13% (4 of 31 female patients) in the ICU group.

As expected, symptoms were correlated with severity of disease (Table 1). In particular, shortness of breath increased with severity of disease, being reported by 209 (37%) of the 569 patients in the community, 118 (65%) of the 181 patients who had been admitted to hospital and 39 (87%) of the 45 patients admitted to an ICU ($p < 0.001$).

Antiviral therapy was known to have been prescribed for 173 (34%) of 511 patients in the community group and 83

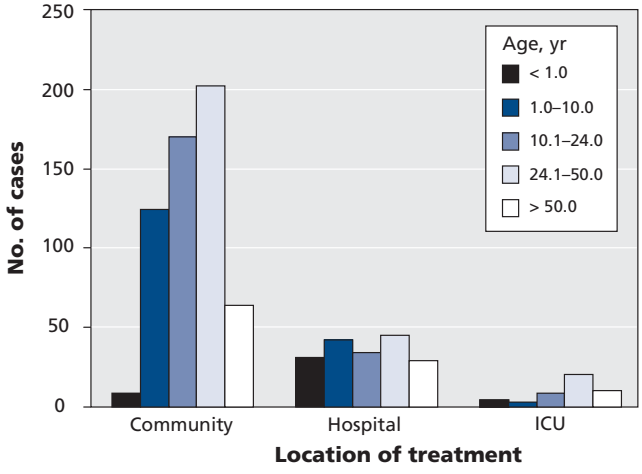

Figure 2: Age-specific distribution of confirmed infections by final location of care. ICU = intensive care unit.

(54%) of 154 who were admitted to hospital, whereas 42 (95%) of 44 patients admitted to the ICU received antiviral therapy ($p < 0.001$). Oseltamivir was used for 274 (97%) of the 282 patients for whom the agent administered was known. Severity of illness increased with increasing interval from onset of symptoms to the start of antiviral therapy (Figure 3). The median interval before initiation of treatment was 2 days (IQR 1–3) for community patients, 4 days (IQR 2–6) for those admitted to hospital but not the ICU and 6 days (IQR 4–9) for those admitted to the ICU ($p < 0.001$). Before the diagnosis of pandemic H1N1 influenza, 239 (42%) of the patients in the community group, 127 (70%) of those admitted to hospital and 29 (64%) of those admitted to an ICU had sought medical care related to their symptomatic illness.

ICU cases v. community controls

The interval from onset of symptoms to initiation of antiviral therapy was the strongest univariable correlate of severity of disease (Table 2). The odds ratio of severe disease among patients with an interval of more than two days was 12.0 (95% CI 4.65–30.7) compared with an interval of up to two days. When the interval from onset of symptoms to treatment

Table 1: Baseline characteristics of patients with laboratory-confirmed 2009 pandemic (H1N1) influenza in Manitoba, 2009

Characteristic	Location of care; no (%) of patients*			
	Community (*n = 569*)	Hospital (other than ICU) (*n = 181*)	ICU (*n = 45*)	*p* value
Age, mean (SD)				
All patients	25.3 (17.5)	23.0 (21.9)	33.4 (19.7)	0.004
Adults (≥ 18 yr)	35.7 (14.0)	39.6 (17.2)	40.5 (14.9)	0.03
Children (< 18 yr)	8.2 (4.4)	4.2 (4.7)	5.1 (6.4)	< 0.001
Sex, female	296 (52)	90 (50)	31 (69)	0.03
Ethnicity, First Nations	*n = 410*	*n = 136*	*n = 42*	
	116 (28)	74 (54)	25 (60)	< 0.001
Income quintile, two lowest combined	*n = 569*	*n = 181*	*n = 45*	
	263 (46)	128 (71)	26 (58)	< 0.001
Rural residence	259 (46)	115 (64)	24 (53)	0.001
Health care worker	51 (9)	7 (4)	4 (9)	0.08
Symptoms				
Fever	469 (82)	150 (83)	42 (93)	0.17
Cough	448 (79)	146 (81)	43 (96)	0.02
Shortness of breath	209 (37)	118 (65)	39 (87)	< 0.001
Myalgia	282 (50)	58 (32)	26 (58)	< 0.001
Gastrointestinal†	271 (48)	79 (44)	23 (51)	0.55
Headache	317 (56)	57 (31)	20 (44)	< 0.001
Any comorbidity‡	201 (35)	103 (57)	34 (76)	< 0.001
Comorbidity (adults only)	*n = 333*	*n = 92*	*n = 34*	
Lung disease	59 (18)	35 (38)	16 (47)	< 0.001
Obesity	NA	NA	21 (62)	NA
Diabetes mellitus	27 (8)	20 (22)	15 (44)	< 0.001
Malignancy	5 (2)	6 (7)	4 (12)	< 0.001
Smoking	76 (23)	26 (28)	13 (38)	0.10
Kidney disease	3 (1)	7 (8)	5 (15)	< 0.001
Pregnancy	9 (3)	18 (20)	4 (12)	< 0.001
Immune suppression	5 (2)	6 (7)	7 (21)	< 0.001
Abuse of alcohol or other substances, injection drug use	19 (6)	9 (10)	7 (21)	0.005

Note: IQR = interquartile range, NA = not available, SD = standard deviation.
*Unless indicated otherwise.
†Nausea, vomiting, diarrhea.
‡Heart disease, diabetes mellitus, tuberculosis, asthma, smoking, neuromuscular disease, kidney disease, malignancy, immune suppression, lung disease, cognitive dysfunction, pregnancy, alcoholism, substance abuse, injection drug use.

was assessed as a continuous variable, the OR was 1.25 (95% CI 1.14–1.38) for every additional day. The presence of a medical comorbidity significantly increased the odds of severe disease (OR 5.70, 95% CI 2.83–11.5). Obesity could not be analyzed because of missing data, as described above. The odds for severe disease were greater among First Nations residents compared with all other ethnicities (OR 3.73, 95% CI 1.94–7.16) and among females compared with males (OR 2.40, 95% CI 1.21–4.77). The univariable odds ratio associated with pregnancy was 3.64 (95% CI 0.86–15.4). The odds of severe disease were greater in the two lowest income quintiles combined than in the three highest income quintiles combined (OR 2.08, 95% CI 1.07–4.07) (Table 2).

In a multivariable logistic model with age, sex, First Nations ethnicity, medical comorbidity, interval from onset of symptoms to initiation of antiviral therapy, urban v. rural status and income quintile group, we found that treatment interval (OR 8.24, 95% CI 2.82–24.1), First Nations ethnicity (OR 6.52, 95% CI 2.04–20.8) and the presence of a medical comorbidity (OR 3.19, 95% CI 1.07–9.52) were associated with increased severity of disease (Figure 4).

In a separate multivariable analysis of hospital controls without admission to an ICU and community controls, we observed consistent associations. The interval from onset of symptoms to initiation of antiviral therapy (OR 3.61, 95% CI 1.79–7.28) and the presence of a medical comorbidity (OR 3.36, 95% CI 2.05–5.49) were significantly associated with admission to hospital. Compared with community controls, the odds of admission to hospital among First Nations individuals was 1.71 (95% CI 0.99–3.00). Age, sex, urban v. rural status and income quintile group were not associated with admission to hospital (without admission to an ICU) relative to community cases.

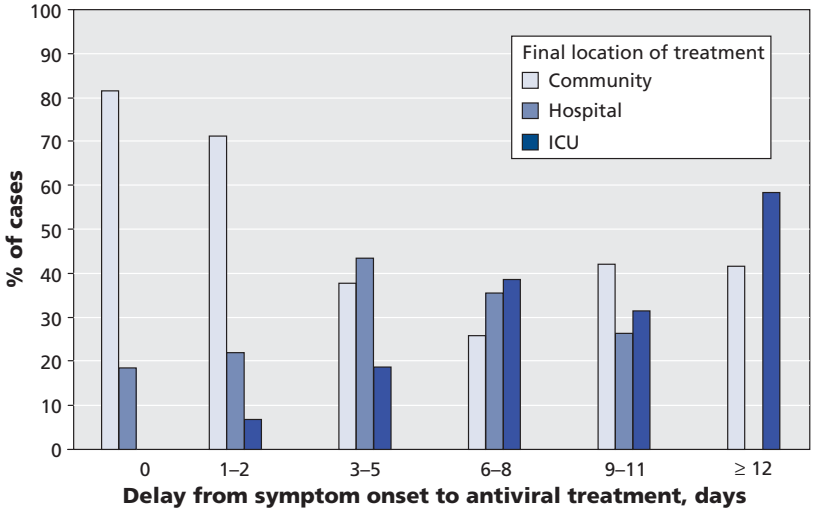

Figure 3: Severity of disease in relation to the interval from onset of symptoms to treatment with antiviral agents. Increasing interval from onset of symptoms to antiviral therapy was associated with increased severity of illness. ICU = intensive care unit.

ICU cases v. hospital controls without ICU admission

Compared with patients under 16 years of age, those 16–45 years of age (OR 3.68, 95% CI 1.47–8.52) and those older than 45 years of age (OR 3.32, 95% CI 1.31–8.44) had greater severity of disease, according to our univariable regression analysis (Table 2). An interval of more than two

Table 2: Univariable predictors of disease severity

	Comparison; OR (95% CI)	
	ICU cases v. community cases	ICU cases v. cases with hospital admission
Age		
16–45 yr v. < 16 yr	2.10 (0.95–4.62)	3.68 (1.47–8.52)
> 45 yr v. < 16 yr	3.29 (1.36–7.96)	3.32 (1.31–8.44)
Female v. male	2.40 (1.21–4.77)	2.61 (1.26–5.41)
Pregnant v. nonpregnant (females aged 16–45 yr)	3.64 (0.86–15.4)	0.33 (0.08–1.38)
Ethnicity		
First Nations v. other	3.73 (1.94–7.16)	1.23 (0.61–2.49)
Missing data v. other	0.33 (0.09–1.13)	0.24 (0.06–0.88)
Any comorbidity*	5.70 (2.83–11.5)	2.34 (1.12–4.91)
Interval from symptom onset to antiviral treatment, > 2 d v. ≤ 2 d	12.0 (4.65–30.7)	3.59 (1.32–9.80)
Rural v. urban	1.37 (0.74–2.51)	0.66 (0.34–1.27)
Income, lowest 2 quintiles v. highest 3 quintiles	2.08 (1.07–4.07)	0.68 (0.33–1.42)

Note: CI = confidence interval, ICU = intensive care unit.
*Heart disease, diabetes mellitus, tuberculosis, asthma, smoking, neuromuscular disease, kidney disease, malignancy, immune suppression, lung disease, cognitive dysfunction, pregnancy, alcoholism, substance abuse, injection drug use.

days from onset of symptoms to initiation of antiviral treatment was correlated with severe disease (OR 3.59, 95% CI 1.32–9.80). A similar result was obtained when treatment interval was analyzed as a continuous variable (OR 1.33, 95% CI 1.18–1.56, for each additional day). Female sex (OR 2.61, 95% CI 1.26–5.41) and presence of an underlying comorbidity (OR 2.34, 95% CI 1.12–4.91) were associated with severe disease. First Nations ethnicity and income quintile group were not associated with ICU admission relative to admission to hospital without admission to an ICU (Table 2).

In our multivariable model, which accounted for age, sex, First Nations ethnicity, medical comorbidity, interval from onset of symptoms to initiation of antiviral therapy, urban v. rural status and income quintile group, we found that First Nations ethnicity (OR 3.23, 95% CI 1.04–10.1) was associated with increased severity of disease (Figure 5). The odds of severe disease associated with interval until treatment was 2.44 (95% CI 0.79–7.50) but did not reach statistical significance (Figure 5).

Interpretation

Main findings

In this cumulative case–control study of laboratory-confirmed cases of 2009 pandemic influenza (H1N1) virus infection among Manitoba residents, severe disease, defined by admission to the ICU, was associated with a longer interval from onset of symptoms to treatment with antiviral therapy and with the presence of an underlying comorbidity relative to those who were not admitted to hospital. After accounting for other potential associations with severity of disease, we found that people of First Nations ethnicity had increased odds of severe disease compared with those of other ethnicities.

Explanation and comparison with other studies

Previous studies have shown that when otherwise healthy individuals with seasonal influenza A are treated with neuraminidase inhibitors within 36–48 hours of onset, the duration of symptoms is decreased by one to two days.[8] Treatment within 12 hours after onset of fever reduces the duration of symptoms by 3.1 days relative to treatment started at 48 hours.[9] Although randomized controlled trials of neuraminidase inhibitors in influenza-infected patients who have been admitted to hospital are lacking, observational studies have suggested that treatment of hospital inpatients who have seasonal influenza can reduce mortality.[10,11]

The ability of neuraminidase inhibitors to prevent severe disease in patients with progressive or persistent symptoms or in patients with comorbidities has not been adequately investigated. However, in a recently published case series of pandemic H1N1 influenza without controls, treatment initiation within two days was associated with a lower risk of admission to the ICU or death.[6] In Mexico, treatment of ICU patients with a neuraminidase inhibitor (v. no treatment) was associated with improved survival (OR 8.5, 95% CI 1.2–62.8).[1]

We found that severity of illness was greater among First Nations people, a finding that persisted after accounting for age, sex, comorbidities, interval from onset of symptoms to treatment, rural residence and income level. This finding is consistent with historical records from the 1918 Spanish influenza pandemic, during which mortality in Aboriginal communities was far higher than in non-Aboriginal commu-

Characteristic	OR (95% CI)
Age, yr	
16–45 v. < 16	1.36 (0.40–4.61)
> 45 v. < 16	1.33 (0.33–5.33)
Sex, female v. male	1.57 (0.59–4.17)
Ethnicity	
First Nations v. other	6.52 (2.04–20.8)
Missing v. other	1.44 (0.26–7.95)
Any comorbidity	3.19 (1.07–9.52)
Symptom onset to antiviral treatment, > 2 days v. ≤ 2 days	8.24 (2.82–24.1)
Location, rural v. urban	0.52 (0.19–1.40)
Income, lowest 2 quintiles v. 3 upper quintiles	1.06 (0.39–2.88)

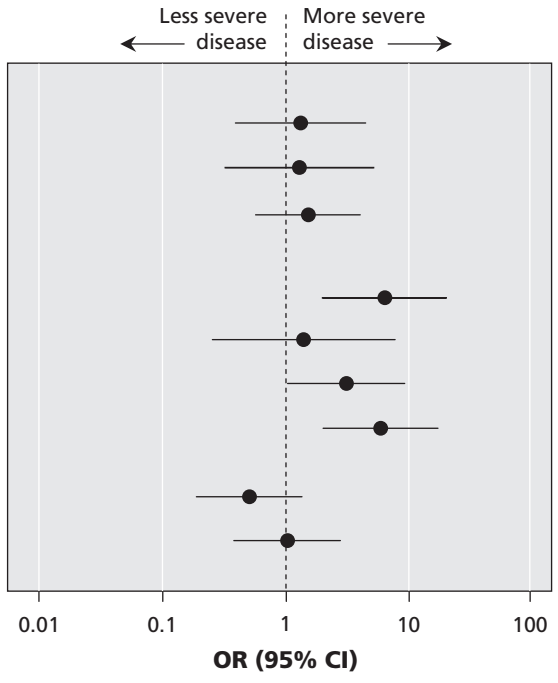

Figure 4: Multivariable correlates of the severity of disease, for comparison between patients cared for in the community and those admitted to an intensive care unit (ICU). CI = confidence interval, OR = odds ratio.

nities.[12,13] Overrepresentation of Aboriginal people in the severe disease cohort (requiring ICU care) was also noted in a recent case series of 2009 influenza (H1N1) virus infection from Australia and New Zealand.[3] As with Aboriginal people in Canada, this group experienced disproportionately higher mortality during the 1918 pandemic.[14]

Common patterns of pandemic H1N1 disease motivate the hypothesis that First Nations peoples may be genetically predisposed to severe infection with the pandemic (H1N1) virus. Host genetics have been shown to affect patients' susceptibility to HIV infection and AIDS[15,16] and their clearance of hepatitis C infection.[17] It is possible that particular human leukocyte antigens or single nucleotide polymorphisms in First Nations or Aboriginal groups affect the acquisition or severity of infection. Intriguing as this hypothesis may be, Canadian Aboriginal people and Australian Aboriginals and Torres Strait Islanders do not share a common ancestry. What they do have in common is a history of colonization, combined with historic and continuing social inequities that have led to significant health disparities.

Limitations

Using a multivariable model, we demonstrated that length of time from onset of symptoms to treatment was the factor most strongly associated with severe disease. In our analyses we tried to control for several potential sources of bias that might affect access to health care; however, it remains unclear whether early diagnosis and treatment were associated with higher-quality or more accessible medical care. Although it is likely that the interval from onset of symptoms to initiation of antiviral therapy could have a direct and causal effect on outcomes, it might also be a marker of other independent causal factors, such as other treatments (e.g., oxygen, fluids and electrolytes, antimicrobials) or other correlates of patient or system-wide characteristics. We were also unable to assess factors relating to education level or household size. In our study, we did not match ICU cases with incident cases of hospital admission without ICU admission or with community controls. If differences in patient presentation (e.g., because of public awareness) or access to care existed, or if treatment decisions differed over the course of the epidemic, these factors might have introduced bias that remained unaccounted for by our analyses. Nonetheless, the brevity of the local epidemic and the relatively uniform distribution of cases and controls throughout the course of the epidemic would have minimized this potential source of bias.

With regard to the association between comorbidities and severity of disease, it is possible that the presence of a comorbid condition that makes admission to the ICU more likely might also have made ascertainment of virologic infection more likely, thus producing an inflated estimate of any potential association. With regard to our study, the relative impact or the direction of this type of selection bias, known as Berksonian bias, is uncertain. Moreover, this type of bias may be paradoxical and may result in a falsely negative association when both the exposure and the disease increase the chance of selection.[18] On June 26, 2009, Manitoba Health released recommendations for treatment of influenza (H1N1) virus infection that encouraged treatment of individuals with risk factors and those with abnormal vital signs. As a result of these guidelines, comorbidities and risk factors such as First Nations status may be overrepresented in the community

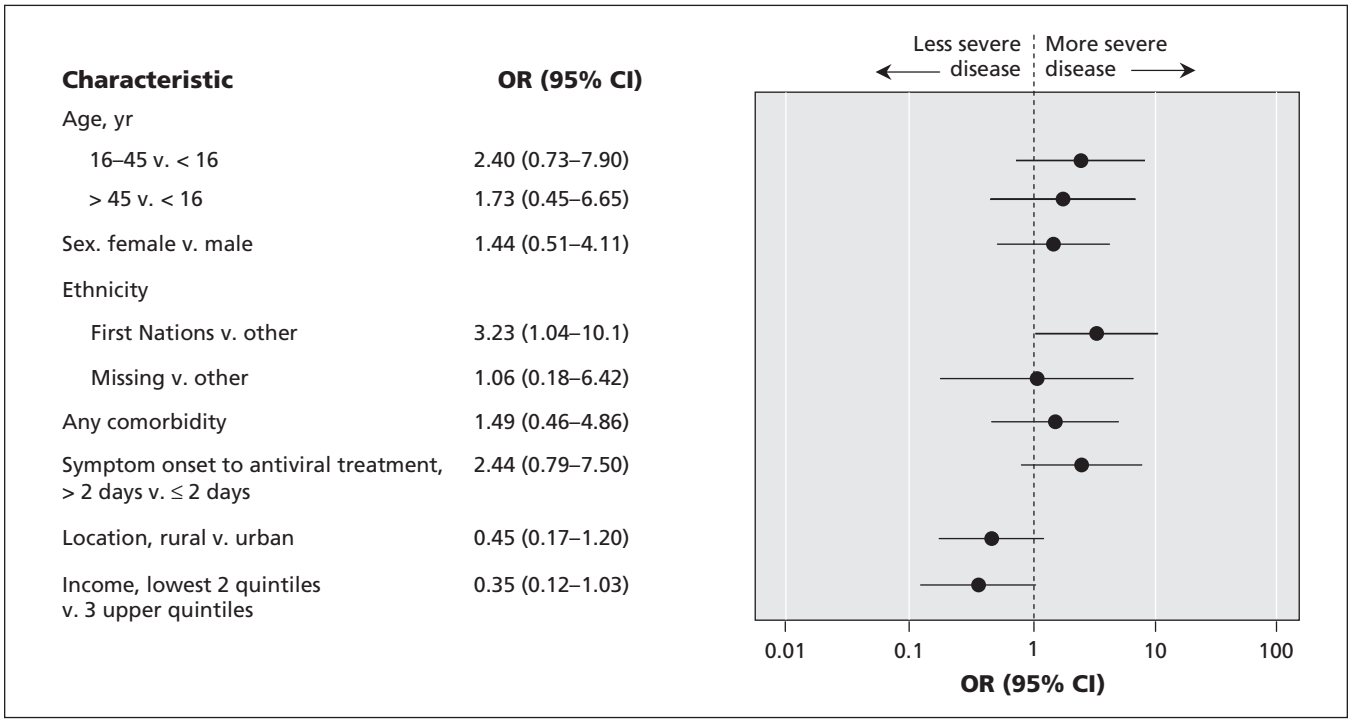

Figure 5: Multivariable correlates of the severity of disease, for comparison between patients admitted to hospital but not to an intensive care unit (ICU) and those admitted to an ICU. CI = confidence interval, OR = odds ratio.

cohort, which could result in an underestimation of the associated risks.

Although our study demonstrated an association between First Nations ethnicity and the odds of severe disease, it is possible that this increased risk reflects uncontrolled confounders such as housing or living conditions, income adequacy, diet, additional underlying comorbidities or access to health care resources.

At the peak of the 2009 influenza (H1N1) epidemic in Manitoba, laboratory testing was recommended and given priority for patients who had been admitted to hospital with suspected or probable more severe disease. Even when testing was offered to all, there were probably numerous individuals in the community with mild disease who never sought medical attention and/or were not tested. As a result, the actual infection rate (the attack rate) and the seroprevalence rate within the province of Manitoba have not been accurately measured. Differential testing of the groups in our study (ICU v. hospital admission without ICU admission or community) may represent a source of information bias; however, an analysis of our two control groups (hospital admission without ICU admission v. community) demonstrated consistent associations.

Conclusions

The severity of illness among patients infected with pandemic H1N1 influenza was associated with the length of time from onset of symptoms to treatment with antiviral therapy and with the presence of underlying medical comorbidities, relative to controls not admitted to hospital. First Nations ethnicity was associated with severe disease, relative to other ethnic groups. These data may have implications for proactive public health and primary care using outreach methods at the community level, whether for public health education, prioritization of vaccination efforts or strategies for antiviral treatment.

This article has been peer reviewed.

Competing interests: None declared.

Contributors: All authors contributed to the study design. Steve Doucette, Ryan Zarychanski and Tammy Stuart were involved in analyzing the data. Ryan Zarychanski and Tammy Stuart drafted the original manuscript. All authors were involved in revisions of the manuscript for significant intellectual content, and all approved the final version submitted for publication.

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REFERENCES

1. Dominguez-Cherit G, Lapinsky SE, Macias AE, et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA* 2009;302:1880-7.
2. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009;302:1872-9.
3. Webb SA, Pettila V, Seppelt I, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 2009;361:1925-34.
4. Intensive-care patients with severe novel influenza A(H1N1) virus infection — Michigan, June 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:749-52.
5. Hanshaoworakul W, Simmerman JM, Narueponjirakul U, et al. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. *PLoS One* 2009;4:e6051.
6. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* 2009;361:1935-44.
7. Manitoba Centre for Health Policy, University of Manitoba. Concept: construction of census income quintiles. Winnipeg (MB): The Centre; 2008. Available: http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1056 (accessed 2009 Nov. 19).
8. Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med* 2005;353:1363-73.
9. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother* 2003;51:123-9.
10. McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis* 2007;45:1568-75.
11. Lee N, Cockram CS, Chan PK, et al. Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. *Clin Infect Dis* 2008;46:1323-4.
12. Graham-Cumming G. Health of the original Canadians, 1867–1967. *Med Serv J Can* 1967;23:115-66.
13. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918–1920 "Spanish" influenza pandemic. *Bull Hist Med* 2002;76:105-15.
14. Cleland-Burton J. Disease among the Australian Aborigines. *J Trop Med Hyg* 1928;6:65-72.
15. Gonzalez E, Kulkarni H, Bolivar H, et al. The influence of CCL3L1 gene-containing segmental duplications on HIV-1/AIDS susceptibility. *Science* 2005;307:1434-40.
16. Hardie RA, Luo M, Bruneau B, et al. Human leukocyte antigen-DQ alleles and haplotypes and their associations with resistance and susceptibility to HIV-1 infection. *AIDS* 2008;22:807-16.
17. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 2009;461:798-801.
18. Rothman K, Greenland S, Lash T. Validity in epidemiologic studies. In: *Modern epidemiology*. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2008.

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