Severe respiratory illness of unexplained etiology during the 2009 influenza pandemic: Analysis of Clinical Features and Outcomes

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ABSTRACT
During the 2009 H1N1 pandemic, 99 severe respiratory illness (SRI) cases were reported in Manitoba. The cause of illness was often not established. Many of these cases may have been unidentified pH1N1. We conducted a chart audit of all severe SRI cases and compared their demographic and clinical characteristics to severe pH1N1 cases. 73 of the 170 cases reviewed were confirmed pH1N1, 53 were SRI with an identified cause, and 44 were SRI with no identified cause. Unexplained SRI cases were similar to pH1N1 cases in terms of risk factors, geographic and temporal distribution, clinical presentation and outcomes. We found that unexplained SRI cases often resembled severe pH1N1 cases, suggesting that these cases were at least in part caused by undiagnosed pH1N1. The overall impact of the pandemic may have been underestimated, especially among the most severely affected indigenous and northern communities.

Introduction
The first cases of influenza A(H1N1)pdm09 (hereafter pH1N1) in Canada were detected among a group of children from Nova Scotia on April 23, 2009 after a school trip to Mexico. During the pandemic’s first wave, the central province of Manitoba was second only to Mexico as the worst hit jurisdiction in the northern hemisphere, accounting for 50% of pH1N1-related intensive care (ICU) admissions reported in Canada. This is despite the fact that out of 170 cases admitted to ICUs with severe respiratory illness (SRI) suspicious for pH1N1 infection, only 71 cases were laboratory-confirmed as pH1N1. The rest did not test positive for the virus. No alternate cause for the illness was found in most instances, suggesting that the virus may have been the cause of illness but was not detected using the standard RT-PCR test used at the time. Several hypotheses have been proposed to explain this presentation but they have yet to be explored in detail.

In response to the wave of SRI cases in the early days of the pandemic, public health authorities established an enhanced province-wide surveillance program mandating that all SRI cases are reported and investigated by public health nurses using a standard questionnaire to gather demographic, clinical and risk factor information. Using this information, we identified all SRI cases and conducted a chart audit to obtain additional clinical and laboratory information. In this paper, we describe the epidemiologic and clinical features of these cases and examine the hypothesis that many of the SRI patients who lacked an alternative etiology may have actually been unidentified pH1N1 cases.

Results
By February 2010, 2,674 confirmed cases of pH1N1 infection were reported in the province (905 cases in the first wave, 1,769 in the second). Of confirmed cases, 14% (n = 383) cases were hospitalized and 3% (n = 71) were admitted to ICU due to pH1N1 (Fig. 1). Another 99 patients were initially classified as SRI cases. Overall, 170 patients were classified as either severe pH1N1 or SRI cases, corresponding to an overall provincial rate of 19 cases per 100,000 person-years (Table 2). This rate was twice as high in the first wave compared with the second (23 vs 12 cases/100,000 person-years).

After review, 53 (31%) of the 170 cases were found to have an alternate diagnosis and were classified as explained SRI whereas 73 (43%) were categorized as severe pH1N1 cases (2 SRI cases were found to have been diagnosed with pH1N1 based on RT-PCR results; for all subsequent analyses, these are grouped with the severe pH1N1 group). The remaining 44 (26%) patients were categorized as unexplained SRI cases. In the first wave, 46 of 82 cases (56%) initially reported as SRIs were classified as explained SRI; this was the case for 7 of 15 cases (47%) in the second wave.

In the first wave, in all 3 categories, there were more females than males and most cases occurred in the 16–64 age group (Table 2). Among adults, the rate of severe pH1N1 was highest in the 36–45 age group (11/100,000 person-years) and lowest among those over age 65 (3/100,000 person-years). Compared to other age groups, children (≤16 years) were more likely to have been misreported as SRIs rather than severe pH1N1; 82%
of SRI cases reported among children in the first wave were found to have an alternate diagnosis after review.

In the first wave, First Nations people represented the largest percentage of both severe pH1N1 (52%) and unexplained SRI (42%) cases (Table 2). Controlling for age, rates of severe pH1N1, unexplained SRI and explained SRI (33, 18 and 22 per 100 000 person-years, respectively) were 3 to 5 times higher in the north (where the majority of residents are of First Nations descent) compared with southern regions (Table 2). Conversely, in the second wave, Caucasians made up larger proportions of severe pH1N1, unexplained SRI and explained SRI groups (52, 25 and 57%, respectively) (Table 2). Also in contrast to the first wave, the highest age-adjusted rates of severe pH1N1 and unexplained SRI were seen in the rural south (Table 2).

Clinical features and risk factors

In both waves (Table 3), all cases of severe pH1N1 met the ILI case definition, while only 13% of explained SRI and 36% of unexplained SRI cases did so. Fever was present in fewer patients in the explained SRI group compared with the unexplained SRI and severe pH1N1 groups, as were shortness of breath, cough and myalgias.

Minimal differences in the presence of underlying chronic conditions were seen between the 3 groups, though explained SRI cases were less likely to have 3 or more chronic conditions or to have diabetes or obesity, and more likely to have heart disease. Asthma was less common in the explained SRI and unexplained SRI groups compared with the severe pH1N1 group. Of the 7 cases (4%) pregnant at the time of admission across

Table 1. Number (%) of severe pH1N1 and SRI by wave, category and demographic characteristics, Manitoba residents.

|                      | Wave 1 |                      | Wave 2 |                      | Total |
|----------------------|--------|----------------------|--------|----------------------|-------|
|                      | Severe pH1N1 | Unexplained SRI | Explained SRI | Severe pH1N1 | Unexplained SRI | Explained SRI | Severe pH1N1 | Unexplained SRI | Explained SRI |
| Total                | 48     | 36                   | 46      | 25                   | 8      | 7                    | 73           | 44                   | 53         |
| Age                  |        |                      |         |                      |        |                      |              |                      |            |
| < 16                 |        |                      |         |                      |        |                      |              |                      |            |
| 16–64                | 10     | (20.8)               | 3       | (8.3)                | 14     | (30.4)               | 3            | (12.0)              | 3          | (42.9)              |
| 65+                  |        |                      |         |                      |        |                      |              |                      |            |
| Mean Age             | 38.3   | 47.9                 | 36.9    |                      | 39.0   | 36.4                 | 36.9         |                      | 38.5       | 45.8                 | 35.3       |
| Gender               |        |                      |         |                      |        |                      |              |                      |            |
| Male                 | 15     | (31.3)               | 16      | (44.4)               | 20     | (43.5)               | 9            | (36.0)               | 4          | (50.0)               | 3          | (42.9)               | 24         | (32.9)               | 20         | (45.5)               | 23         | (43.4)               |
| Female               | 33     | (68.8)               | 20      | (55.6)               | 26     | (56.5)               | 16           | (64.0)               | 4          | (50.0)               | 4          | (57.1)               | 49         | (67.1)               | 24         | (54.5)               | 30         | (56.6)               |
| Ethnicity            |        |                      |         |                      |        |                      |              |                      |            |
| Caucasian            | 12     | (25.0)               | 10      | (27.8)               | 14     | (30.4)               | 13           | (52.0)               | 2          | (25.0)               | 4          | (57.1)               | 25         | (34.2)               | 12         | (27.3)               | 18         | (34.0)               |
| Métis                | 1      | (2.1)                | 2       | (5.6)                | 2      | (4.3)                | 0            | (0.0)                | 2          | (25.0)               | 0          | (0.0)                | 1          | (1.4)                | 4          | (9.1)                | 2          | (3.8)                |
| First Nations        | 25     | (52.1)               | 15      | (41.7)               | 17     | (37.0)               | 3            | (12.0)               | 1          | (12.5)               | 3          | (42.9)               | 28         | (38.4)               | 16         | (36.4)               | 20         | (37.7)               |
| Other                | 3      | (6.3)                | 4       | (11.1)               | 3      | (6.5)                | 1            | (4.0)                | 1          | (12.5)               | 0          | (0.0)                | 4          | (5.5)                | 5          | (11.4)               | 3          | (5.7)                |
| Unknown              | 7      | (14.6)               | 5       | (13.9)               | 10     | (21.7)               | 8            | (32.0)               | 2          | (25.0)               | 0          | (0.0)                | 15         | (20.5)               | 7          | (15.9)               | 10         | (18.9)               |
| Region               |        |                      |         |                      |        |                      |              |                      |            |
| Winnipeg Health Region | 20     | (41.7)               | 17      | (47.2)               | 28     | (60.9)               | 11           | (44.0)               | 3          | (37.5)               | 4          | (57.1)               | 31         | (42.5)               | 20         | (45.5)               | 32         | (60.4)               |
| Northern RHAs*       | 18     | (37.5)               | 9       | (25.0)               | 11     | (23.9)               | 2            | (8.0)                | 0          | (0.0)                | 2          | (28.6)               | 20         | (27.4)               | 9          | (20.5)               | 13         | (24.5)               |
| Rest of province     | 10     | (20.8)               | 10      | (27.8)               | 7      | (15.2)               | 12           | (48.0)               | 5          | (62.5)               | 1          | (14.3)               | 22         | (30.1)               | 15         | (34.1)               | 8          | (15.1)               |

*Northern RHAs include North Eastman, Norman, Burntwood and Churchill RHAs
Table 2. Number (%) of severe pH1N1 and SRI by wave, category and clinical features, Manitoba residents.

| Presenting Symptoms and Signs | Wave 1 |  | Wave 2 |  | Total |  |
|-------------------------------|--------|---|--------|---|-------|---|
|                               | Severe pH1N1 | Unexplained SRI | Explained SRI | Severe pH1N1 | Unexplained SRI | Explained SRI | Severe pH1N1 | Unexplained SRI | Explained SRI |
| Meets ILI case definition     | 48     | 36 | 46     | 25     | 8     | 7     | 73     | 44     | 53     |
| Cough                         | 47 (97.9) | 13 (36.1) | 6 (13.0) | 25 (100.0) | 3 (37.5) | 1 (14.3) | 72 (98.6) | 16 (36.4) | 7 (13.2) |
| Fever                         | 36 (75.0) | 27 (75.0) | 29 (63.0) | 19 (76.0) | 8 (100.0) | 5 (71.4) | 55 (75.3) | 35 (79.5) | 34 (64.2) |
| Myalgia                       | 40 (83.3) | 30 (83.3) | 29 (63.0) | 22 (88.0) | 6 (75.0) | 7 (100.0) | 62 (84.9) | 36 (81.8) | 36 (67.9) |
| Shortness of breath           | 12 (25.0) | 10 (27.8) | 5 (10.9) | 3 (32.0) | 3 (37.5) | 0 (0.0) | 20 (27.4) | 13 (29.5) | 5 (9.4) |
| Mortality                     | 36 (75.0) | 33 (91.7) | 28 (60.9) | 22 (88.0) | 6 (75.0) | 3 (42.9) | 58 (79.5) | 39 (86.6) | 31 (58.5) |
| Death linked to respiratory illness of all deaths | 6 (12.5) | 4 (11.1) | 2 (4.3) | 1 (4.0) | 1 (12.5) | 2 (28.6) | 7 (9.6) | 5 (11.4) | 4 (7.5) |
| Protective Factors            | Total   | 48 | 36 | 46 | 25 | 8 | 7 | 73 | 44 | 53 |
| Received trivalent influenza vaccine in 08/09 | 10 (20.8) | 10 (27.8) | 12 (26.1) | 5 (20.0) | 0 (0.0) | 3 (42.9) | 15 (20.5) | 10 (22.7) | 15 (28.3) |
| Received trivalent influenza vaccine in 09/10 | not available | 4 (16.0) | 0 (0.0) | 0 (0.0) | 4 (5.5) | 0 (0.0) | 0 (0.0) | 3 (4.1) | 0 (0.0) | 1 (1.9) |
| Received the Pandemic H1N1 influenza vaccine | not available | 3 (12.0) | 0 (0.0) | 1 (14.3) | 3 (4.1) | 0 (0.0) | 1 (1.9) | 6 (8.3) | 1 (2.3) | 0 (0.0) |
| Treated with antivirals       | Antivirals started within 2 d of onset | 40 (83.3) | 30 (83.3) | 25 (54.3) | 19 (76.0) | 7 (87.5) | 5 (71.4) | 59 (80.8) | 37 (84.1) | 30 (56.6) |

Table 3. Provincial case definitions.

| Influenza-like illness (ILI) | Severe ILI | Severe respiratory illness (SRI) |
|-----------------------------|------------|----------------------------------|
| Fever >38 C AND cough AND one or more of sore throat, arthralgias, myalgias or prostration.* | Acute onset of respiratory illness with fever and cough and one or more of the following: sore throat, arthralgias, myalgias or prostration which could be due to influenza virus, and include complications such as encephalitis or other severe and life-threatening complications.** |
| First wave ILI symptoms with worsening cough, dyspnea, atypical pneumonia on CXR or Acute Respiratory Distress Syndrome. Admission to hospital is required to support these patients.*** | All of the following: • Admission to hospital • Fever >38 C • New onset of (or exacerbation of chronic) cough or breathing difficulty • Admission to ICU/other area of the hospital where critically ill patients are cared for OR mechanical ventilation with evidence of severe illness progression (either radiographic evidence of infiltrates consistent with pneumonia or a diagnosis of Acute Respiratory Distress Syndrome/severe ILI) • No alternate diagnosis within the first 72 hours of hospitalization |
| Second wave                  |  |

* Fever may be muted in patients under age 5, those undergoing cancer and blood disorder treatments, or with receipt of antipyretics, corticosteroids or immunosuppressive drugs. In children under age 5, gastrointestinal symptoms may also be present and cough may not be prominent; children may also present with respiratory compromise, altered mental status and neurologic findings, or evidence of sepsis. Neonates may present with apnea, cyanosis, poor feeding, lethargy and sepsis.

** (In children under age 5, cough may not be prominent and gastrointestinal symptoms may also be present. In patients under 5 or over 65, fever may not be prominent.)

*** This definition was operationalized in different ways but usually requiring fever and cough or shortness of breath AND admission to ICU or ventilation.(

Both waves, 6 were severe pH1N1 cases. More explained SRI and unexplained SRI than severe pH1N1 cases reported lifestyle risk factors, including current smoking and alcohol abuse.

Overall 3-quarters of all cases received anti-viral treatment (Table 3). Fewer explained SRI cases received antivirals than unexplained SRI and severe pH1N1 cases. No explained SRI cases and only 2.3% of unexplained SRI cases received antivirals within 48 hours of symptom onset, while 16% of severe pH1N1 cases did.

Only 24% of all cases received the 2008/09 seasonal influenza vaccine (Table 3). In the first wave, this included similar proportions of severe pH1N1 (21%), unexplained SRI (28%) and explained SRI (26%) cases. In the second wave when the 2009/10 seasonal and pandemic influenza vaccines were available, few cases (5% or less) in any group had received them.

A total of 25 cases died, 20 during the first wave and 5 during the second; the overall case-fatality rate was about 15% in all 3 groups during the first wave (Table 3). In this wave, the majority of deaths in the severe pH1N1 (75%) and unexplained SRI (80%) groups were attributed to a respiratory illness, while only 29% of the explained SRI group deaths were so attributed.

Diagnostic testing of SRI cases

In 15% of explained SRI and 11% of unexplained SRI cases, there was no evidence that the patient was tested for pH1N1. Of all unexplained SRI cases, 61% were tested using either nasopharyngeal swab along with one of endotracheal aspirate or bronchoalveolar lavage. Another 25% were tested using NPS.
only, and one was tested using ET+BAL. Virtually all tests were performed at Cadham Provincial laboratory using a real-time reverse transcriptase polymerase chain reaction (RT-PCR) test developed at the National Microbiology Laboratory (2).

More severe pH1N1 cases were tested within the recommended maximum of 5 days from symptom onset than either explained SRI or unexplained SRI cases, and within the ideal maximum of 48 hours from symptom onset. There were no significant differences in the modalities of virologic testing.

**Discussion**

We found that unexplained SRI cases often resembled severe pH1N1 cases more than they resembled the explained SRI cases. For instance, unexplained SRI incidence tended to align both temporally and geographically with severe pH1N1 incidence, while explained SRI cases were less so aligned. There were also more similarities in presenting symptoms and outcomes between the severe pH1N1 and unexplained SRI groups than between the unexplained SRI and explained SRI groups. Some patterns of underlying conditions (especially the presence of 3 or more chronic conditions, diabetes and obesity) followed similar trends.

These similarities suggest that at least some of the unexplained SRI cases may have actually been caused by undiagnosed pH1N1. Recommended testing of SRI cases suspected of having pH1N1 emphasized gathering both nasopharyngeal swabs and either endotracheal aspirate or bronchoalveolar lavage within 5 days (ideally within 48 hours) of symptom onset.4 Given that many unexplained SRI cases were not tested at all, and that few of the tests were performed within the recommended time frame, it is easy to see how pH1N1 may have been missed.

Determination of the etiology of unexplained SRI cases may also have been affected by limitations of the diagnostic tests themselves. Even after the US Center for Disease Control completed (as part of routine surveillance) a thorough review of possibly infectious cases resulting in disease or critical illness, including comprehensive laboratory testing, many cases remained unexplained.5

Ong et al found that the presence of fever and cough were the best variables in distinguishing pH1N1 from other respiratory illnesses; cases with fever and cough were 65 and 2.5 times, respectively, more likely to test positive for pH1N1 that those without.6 Boivin et al similarly found that with seasonal influenza known to be circulating in the community, the combination of fever and cough had a positive predictive value of 86.8%.7 In our study, 82% of unexplained SRI cases had fever and 80% had cough; these proportions were higher than in the explained SRI cases (68 and 64%), and similar to those in the severe pH1N1 group (85 and 75%). This also supports the hypothesis that many unexplained SRI cases may have been caused by undiagnosed pH1N1.

The disproportionate impact of pH1N1 and other influenza pandemics on First Nations and northern communities has been previously noted, but the reasons for this are not fully understood. If in fact pH1N1 was present but not identified in unexplained SRI cases, many of whom were of First Nations descent and resided in northern areas, then these communities may have been harder hit by this pandemic than has been previously appreciated. Planning for future pandemics should account for the possibility that those most severely impacted might initially be far away from investigation and management services.

**Limitations**

One limitation in our study is the change in SRI case definition after the first wave to exclude patients in whom an alternate cause for symptoms was found within 72 hours of admission. This may have resulted in a decrease in the number of SRI cases reported in the second wave. Another limitation is the relatively small numbers of severe pH1N1 and SRI cases, particularly in the second wave. This led to difficulty in the interpretation of certain results, particularly when cases were stratified by multiple variables. As well, detailed chart audits were conducted only for SRI and not pH1N1 cases. Therefore, some data obtained from the chart audit (e.g., detailed information on all diagnostic tests conducted) were not available for severe pH1N1 cases. Finally, because of the retrospective nature of our investigation, we were unable to conduct further diagnostic testing to confirm the etiology of unexplained SRI cases.

**Methods**

**Study population**

We included all residents of Manitoba who were reported to Manitoba Health as meeting the provincial SRI case definition (Table 1) in the first or second wave of the pandemic. In the first wave (April 15 to October 5, 2009), the case definition required the presence of influenza-like illness (ILI) symptoms with worsening cough, dyspnea, atypical pneumonia on chest X-ray or acute respiratory distress syndrome. ILI was defined as fever and cough and one or more of: sore throat, arthralgia, myalgia or prostration. The case definition was refined during the second wave (October 6, 2009 to January 15, 2010) to exclude patients for whom an alternate cause for illness was established within 72 hours of admission, either clinically or using laboratory methods; this better reflected the widely used operational definition and made it more consistent with the definition recommended by the Public Health Agency of Canada.

**Data sources**

The Manitoba Health Pandemic Influenza Surveillance Database included demographics, laboratory results, and information gathered using the standard pH1N1/SRI provincial case investigation form. Additional laboratory, clinical and risk factor information was obtained from the Winnipeg Regional Health Authority (WRHA) Pandemic Surveillance Database for all cases occurring among Winnipeg residents and those admitted to Winnipeg hospitals, where more than 90% of SRI and severe pH1N1 cases were treated. We merged these databases using Manitoba’s unique Personal Health Identification Number (PHIN). The resulting data set included information
on all cases of severe pH1N1 (n = 71) and SRI (n = 99) reported during the pandemic.

The hospital charts of all cases identified in the merged database underwent a detailed audit to determine if cases met the case definitions and to extract detailed clinical information. The audit was completed in full by a single expert auditor from the WRHA Audit Team who entered all information directly into a custom-built database. Data collected included patient demographics, comorbidities, presenting symptoms, treatments and other interventions, all imaging and laboratory test results, patient outcomes and overall clinical impressions of the attending physicians. A single physician (SMM) reviewed the data to determine whether the case definitions were met.

In addition, information on seasonal and pandemic influenza and pneumococcal immunizations was obtained from the Manitoba Immunization Monitoring System (MIMS) database, which, since 2000, tracked all pediatric and adult vaccines administered to Manitoba residents.10 Information on pregnancy outcomes was obtained from the WRHA postpartum database. Reports from regional medical officers of health who investigated all potential pH1N1-related deaths, were used to establish whether the death was directly related to pH1N1 infection.

Statistical analysis

We categorized reviewed cases into one of 3 groups: severe pH1N1 cases (those who tested positive for pH1N1 by real-time reverse-transcriptase PCR (RT-PCR) or viral culture), explained SRI (SRI cases who after review were found to have an alternate diagnosis other than pH1N1 infection), or unexplained SRI (SRI cases where no cause of illness was found).

The crude incidence rates of explained SRI, unexplained SRI and severe pH1N1 were calculated using the June 2008 mid-point population of the province (N = 1,198,981) as the denominator, and the 95% confidence interval (95% CI) was calculated assuming a Poisson distribution. Wave-specific rates were calculated assuming that the population was exposed to pH1N1 and SRI risk for 25 weeks in the first wave and for 14.5 weeks in the second wave, whereas overall rates were calculated assuming that the population was exposed for 40 weeks in total. All rates were reported per 100,000 person-years of presumed exposure. Regional rates were age-standardized to the 2008 Manitoba population (Manitoba Health Population Registry File June 2008). Characteristics of cases in the first wave were often different from those in the second wave; therefore, when appropriate, results are presented by wave. We did not perform statistical inference testing because this analysis was exploratory (hypothesis-generating) rather explanatory (hypothesis-testing).

Conclusion

We found that unexplained SRI cases often resembled severe pH1N1 cases more than they resembled the explained SRI cases, suggesting that these cases were at least in part caused by undiagnosed pH1N1, possibly due to lack of appropriate pH1N1 testing in many cases. The overall impact of the pandemic, in terms of the number of severe cases and health services utilization, may have been underestimated especially among the most severely affected indigenous and northern communities.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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