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Original Article

Statistical estimates of respiratory admissions attributable to seasonal and pandemic influenza for Canada

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Background The number of admissions to hospital for which influenza is laboratory confirmed is considered to be a substantial underestimate of the true number of admissions due to an influenza infection. During the 2009 pandemic, testing for influenza in hospitalized patients was a priority, but the ascertainment rate remains uncertain.

Methods The discharge abstracts of persons admitted with any respiratory condition were extracted from the Canadian Discharge Abstract Database, for April 2003–March 2010. Stratified, weekly admissions were modeled as a function of viral activity, seasonality, and trend using Poisson regression models.

Results An estimated 1 out of every 6·4 admissions attributable to seasonal influenza (2003–April 2009) were coded to J10 (influenza virus identified). During the 2009 pandemic (May–March 2010), the influenza virus was identified in 1 of 1·6 admissions (95% CI, 1·5–1·7) attributed to the pandemic strain. Compared with previous H1N1 seasons (2007/08, 2008/09), the influenza-attributed hospitalization rate for persons <65 years was approximately six times higher during the 2009 H1N1 pandemic, whereas for persons 75 years or older, the pandemic rate was approximately fivefold lower.

Conclusions Case ascertainment was much improved during the pandemic period, with under ascertainment of admissions due to H1N1/2009 limited primarily to patients with a diagnosis of pneumonia.

Keywords Case ascertainment, data analysis, empirical research, hospital admissions, statistical models, seasonal and pandemic, influenza.

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Introduction

As many respiratory viruses are responsible for influenza-like symptoms and laboratory testing is not routine, estimates of the disease burden associated with influenza have traditionally been based on statistical methods. The substantial burden due to influenza was first recognized as a result of Serfling's statistical estimates[1] in the 1960s. Influenza continues to cause annual outbreaks of respiratory illness accounting for workplace absenteeism rates of 5–20% annually[2] as well as a significant annual morbidity[3] and mortality[4] burden in Canada,[5] the United States[6,7] and internationally.[8–11] These and other studies have identified that only a small fraction of the burden attributable to seasonal influenza is actually laboratory confirmed. Throughout the 2009 pandemic period, priority was given in Canada to the use of laboratory testing for the diagnosis of influenza in hospitalized patients. Despite similar recommendations in the United States, the US Centers for Disease Control and Prevention (CDC) aware that incomplete testing and false negative results[12] were contributing to a significant underestimation of the true H1N1/2009 burden,[13] started correcting for under-ascertainment using a multiplier model as of July 2009.[14] In December 2009, the World Health Organization (WHO) recommended that the burden of the pandemic be assessed using statistical methods similar to those used to assess the burden of seasonal influenza.[13] Post-pandemic, the WHO has identified the need to analyze pandemic-related data to provide guidance for future pandemic planning at both the local and global scale.[15]

With this objective in mind, we estimated the number of excess respiratory admissions attributable to seasonal and pandemic influenza from a Canadian database of hospital discharges;[16] reviewed the impact of different statistical models on these estimates; compared age-specific hospitalization rates for the H1N1/2009 pandemic strain to rates for the previous seasonal strains of H1N1 and for seasonal influenza in general; estimated the under-ascertainment rate and identified diagnostic codes that exhibited statistically significant excesses associated with the pandemic period.

Methods

Overview

As influenza activity is concentrated over a relatively short period of time and results in considerable disease burden, an excess strongly associated with the timing of peak influenza activity is often evident in a plot of weekly admissions to hospital for respiratory conditions or all-cause mortality. This pattern suggests the suitability of statistical methods to estimate the hidden burden. Although differences between some published estimates of the influenza burden have been attributed to the use of different methods,[17] there seems to be a general consensus that estimates are robust to some variation in methods (Serfling versus regression) and choice of proxy variables for influenza.[18] Proxy variables are not available for all major viruses contributing to the burden of respiratory illnesses and the question of the impact of ignoring these other viruses in this modeling approach is a valid one, and a common one. In general, respiratory viruses other than influenza can be ignored without significantly altering the estimated burden attributed to influenza in an adult population.[3] However, as other respiratory viruses such as respiratory syncytial virus (RSV) and parainfluenza (PIV) account for a significantly larger disease burden in a pediatric population, estimates of the burden attributed to influenza for children and infants is less precise than for adults.[19]

Sources of data

Hospital discharge records for patients admitted to an acute-care hospital for urgent care with a respiratory diagnosis (J00-J99) in any of the 25 diagnostic fields were extracted from the Canadian Institute of Health Information (CIHI) patient-specific Discharge Abstract Database (DAD)[16] for the period September 2003 to March 2010, a period when most provinces were using the *International Classification of Disease, Tenth Modification* (ICD-10),[20] Canadian version (ICD-10-CA)[21] for chart abstraction. Manitoba converted to ICD-10 in April 2004, and the province of Quebec does not participate in the DAD. Hence, the DAD includes approximating 75% of all acute-care hospital separations in Canada. In May 2009, CIHI advised hospitals to classify any lab-confirmed H1N1 cases to ICD-10-CA code J09, and modified this guidance in November 2009 to also accept cases where a clinical diagnosis of H1N1 had been made in the patient's chart, regardless of whether there was a supporting laboratory report.[22] Admissions were stratified by age, diagnostic category, or discharge status, and aggregated to weekly levels. Categories of interest included the presence or absence of pneumonia and whether the diagnosis most responsible for the length of stay (MRD) was a respiratory or non-respiratory condition. Admissions with the ICD-10 codes J10.0 and J11.0 (pneumonia with influenza) as well as J12-J18 were considered pneumonia admissions. Unless otherwise specified, 'respiratory admissions' refers to cases with any diagnosis of a respiratory condition. Statistical estimates of workplace absenteeism rates due to influenza[2] were used to approximate the expected clinical attack rate among persons admitted to hospital specifically for non-respiratory reasons.

As the seasonality of admissions with a J11 code [influenza or influenza-like illness (ILI), virus not identified] was distinct from the seasonality of J10/J09 coded admissions (J10 corresponds to influenza virus identified and J09 was used for the identification of the pandemic H1N1), J11 coded admissions were considered to be due to a mix of influenza or other respiratory viruses. Hence, hospital admissions coded to J10/J09 as the primary diagnosis were used as a proxy for the weekly level of influenza activity. Admissions coded to J12.1 (viral pneumonia due to RSV) were used as a proxy for RSV activity. For infants and young children, other viruses are also responsible for a significant proportion of respiratory admissions. In particular, the seasonal pattern of croup admissions resembled the pattern of human PIV-1 with a bi-annual pattern of peaks in the fall in alternating years.[23] Hence, to facilitate modeling of respiratory admissions in young children, the number of weekly croup admissions (J05) in infants and children under the age of 3 years and without any mention of influenza was used as a proxy variable for PIV-1, although this proxy would also include other viruses.[19,24]

Population denominators were obtained from Statistics Canada census and inter-census population estimates.[25]

Analysis

Stratified weekly admissions were modeled as a function of viral activity, seasonality, and trend using Poisson regression models similar to those used for previously published estimates of the influenza burden in Canada.[2–4,19] The regression model was fit using SAS Enterprise Guide 4.1 (The SAS Institute, Cary, NC)[26] PROC GENMOD with a Poisson distribution, linear link function and dispersion parameter specified by:

$$ADMS = \sum_{m=1}^{12} \beta_{1,m} Mon_m + \beta_2 \cos(t) + \beta_3 \sin(t) + \sum_{y=2003/04}^{2009/10} \beta_{4,y} FY_y + \beta_5 Pandemic2009 + \beta_6 Holiday + \beta_7 Dec25 + \beta_8 Jan1 + \beta_9 RSV + \beta_{10} PIV1 + \sum_{y=2003/04,\, p=0,1}^{2009/10} \beta_{11,y,p} FY_y * Pandemic2009 * Influ$$

where *ADMS* represents the weekly number of respiratory admissions for the category of interest (respiratory admissions by age group or diagnostic groups or for special categories such as in-hospital deaths), the β_1 parameters account for the baseline seasonality with monthly indicator variables (Mon_m), whereas the sinusoidal terms (with $t = 2\pi$ *week*/52.177457) were included as an alternative approach to describing seasonality, the β_4 parameters account for a general trend with indicator variables for each flu year (FY_y) starting in September, β_5 accounts for any change to baseline admissions resulting from the declaration of a pandemic, the β_6, β_7, β_8 parameters account for the effects of holidays, the last week of December, which includes December 25 (Christmas) and the first week of January, respectively, and the β_9, β_{10}, and β_{11} parameters are multipliers for the proxy variables for RSV (*RSV*), PIV-1 and other viruses associated with croup (*PIV*1), and influenza (*Influ*), respectively. Separate multipliers (β_{11} parameters) were estimated for each flu year (*FY*) and for the spring and fall wave of the 2009 pandemic. The influenza proxy variable *Influ* includes only primary diagnoses of J09 or J10, whereas the base for the multiplier used elsewhere in the article includes all admissions with a J09 or J10 diagnostic code for the specific category and was calculated separately. To ensure that the model was not over fit, results for the full model were compared with results from regression models with fewer explanatory variables. The dispersion parameter was included to account for additional variation due to events not captured by the choice of explanatory variables. As the *ADMS* rates were not of interest to this study, population denominators were not included in the regression model per se. The β_4 parameters for each flu year accounted for the impact of population growth as well as any changes in admission practices.

Influenza-attributed admissions were calculated as the difference between model predicted admissions and the model predicted admissions under the hypothetical absence of influenza. The same proxy variables were used for all regression models to provide the best measure of weekly viral activity. Multipliers were calculated by dividing the estimated number of admissions attributed to influenza by the number of J10/J09 admissions for the appropriate category (for example, age group). Confidence intervals for estimates of influenza-attributed rates were calculated from the coefficient of variation of the corresponding parameter used in the regression model (β_{11}). Hospitalization rates attributable to seasonal (2003–April 2009) and pandemic influenza (May 2009–March 2010) for the study area of DAD participating hospitals were extrapolated to the Canadian population as of 2009. The expected background prevalence of symptomatic influenza among patients admitted specifically for non-respiratory causes was calculated as the average daily admission rate for non-respiratory causes times the duration of clinical illness (2 or 3 days for seasonal and pandemic influenza, respectively) times the average annual clinical attack rate (12% or 13%).[2] H1N1 seasons were identified from annual reports[27] to provide a direct comparison between the 2009 pandemic strain (A/California/7/2009) and previous H1N1 seasons.

Results

Seasonal influenza was associated with an average excess of 35 (95% CI, 31–39) respiratory admissions per 100 000 populations per season from September 2003 to April 2009. The corresponding rate for the H1N1/2009 pandemic was 54 (95% CI, 46–62) per 100 000 population over the pandemic period that included a spring and fall wave. Based on a population of 33·7 million in Canada in 2009, these rates correspond to an estimated 18 000 excess respiratory admissions due to the H1N1/2009 pandemic strain. In comparison, 12 000 (6000–20 000, seasonal range) admissions would have been expected in the 2009/10 season based on the impact of seasonal influenza in previous seasons. Estimated respiratory hospitalization rates due to seasonal influenza varied from a low of 19 (95% CI, 9·7–27) per 100 000 for the 2005/06 season (A/California/7/04) to 58 (95% CI, 48–68) per 100 000 in 2004/05 when two H3N2 strains circulated (A/Fujian/411/02 and A/California/07/04).[28]

Prior to the pandemic period, an influenza virus was identified in the discharge record in an estimated 1 of every 6·8 (95% CI, 6·1–7·6) respiratory admissions attributed to influenza. Influenza or ILI, that is a J10 or J11 code, was noted in 23% of the admissions attributed to influenza. For the pandemic period, the corresponding multiplier was 1·6 (95% CI, 1·4–1·9) and 76% of the respiratory admissions attributed to pandemic influenza had some mention of influenza or ILI. The multiplier associated with deaths among hospitalized patients was estimated at 1·82 (95% CI, 1·33–2·32) for H1N1/2009; down from 12·5 (95% CI, 11·8–13·3) for seasonal influenza.

The H1N1/2009 strain had a strong impact on respiratory admissions for adults aged 20–49 years (Figure 1A). For this age group, seasonality was not well characterized by a sinusoidal distribution and the monthly indicator variables along with holiday variables to account for a spike over the Christmas/New Year holiday period into the first

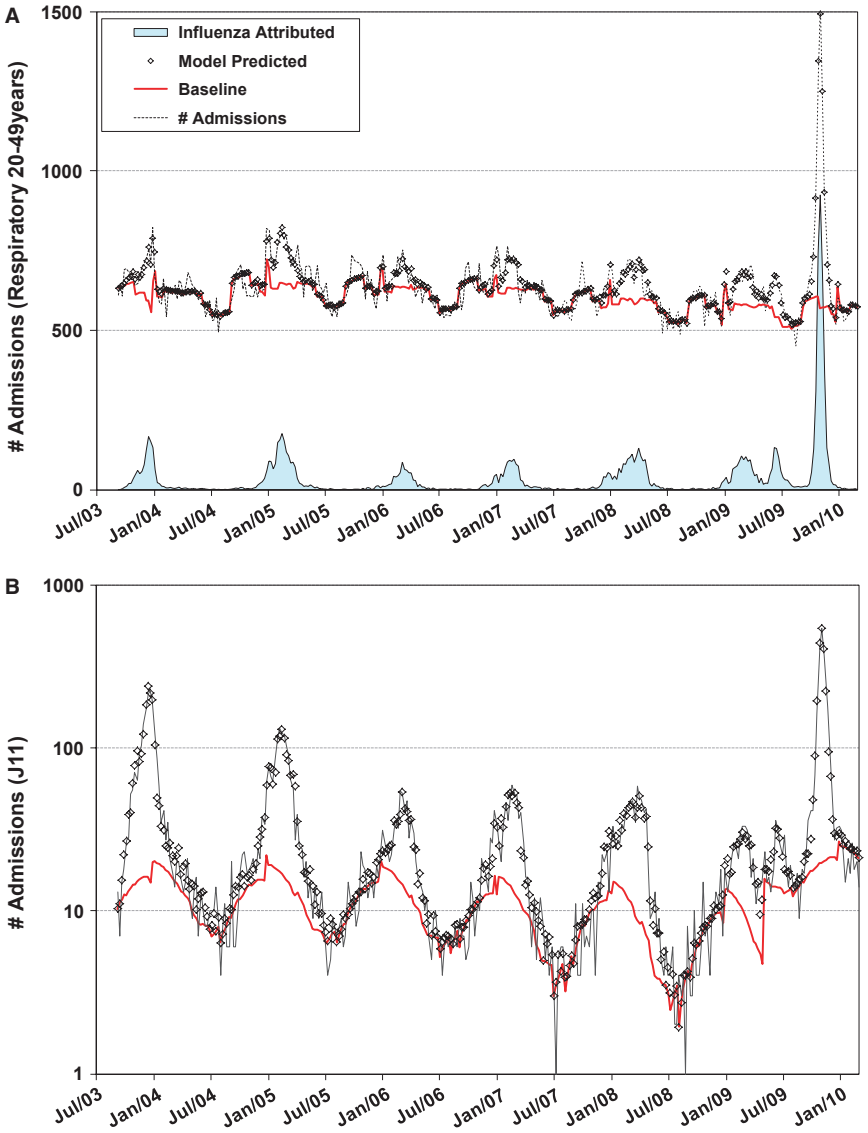

Figure 1. Respiratory admissions to hospital for urgent care, Discharge Abstract Database participating hospitals (Canada, excl Quebec) showing model fit and estimated baseline. (A) Weekly respiratory admissions to hospital for persons aged 20–49 years (·····). The impact of the pandemic strain on younger adults is obvious; the shaded area represents excess admissions attributed seasonal and pandemic influenza, corresponding to annual rates of 11/100 000 and 39/100 000, respectively. The estimated baseline curve (——) accounts for seasonality and secular trends inherent in all respiratory admissions for this age group. Seasonality in this population was not well characterized by the sinusoidal function, and a noticeable spike over the extended Christmas holiday period into the 1st week of January can be observed. There was no increase in baseline respiratory admissions in this age group over the pandemic period. Model predicted values (◇) correspond closely to the actual number of admissions (·····). (B) Weekly admissions to hospital with any mention of J11 (influenza, virus not identified). The weekly number of admissions is shown on a log scale to highlight the characteristics of the model estimated baseline. The baseline (——) corresponds to the expected number of background admissions coded to J11 [diagnosed as influenza-like illness (ILI)] – that is ILI admissions due to other viruses. Once the pandemic was announced, J11 admissions increased despite efforts to test all suspected H1N1/2009 admissions. In addition to significant increases in admissions likely due to H1N1/2009, the fitted model suggests that there was also a significant increase in the diagnosis of ILI among persons admitted with other acute respiratory infections, as a large part of the increase was not associated with the level of H1N1/2009 activity (jump in baseline starting in May 2009). The model predicted number of J11 admissions closely follows the actual number of J11 admissions. Note that while the use of a log scale was helpful to illustrate variation in the estimated baseline, it also distorted the visual perception of the disease burden.

week of January were needed to fully characterize the seasonal pattern. No increase in baseline respiratory admissions was observed over the pandemic period. In contrast, the sinusoidal curve captured most of the seasonal variation in admissions with a clinical diagnosis of influenza or ILI (Figure 1B). However, inclusion of monthly indicator variables suggests that baseline diagnoses of ILI are actually slightly higher in the winter months (Figure 1B) than predicted by sinusoidal seasonality. Once the pandemic was announced, a sharp increase in the use of J11 for non-influenza-related admissions is noted in the baseline. The model fit is shown on a log scale to highlight these details in the baseline estimate. For seasonal influenza, 58% of admissions coded to J11 annually were attributable to influenza compared with 71% for H1N1/2009 (prorated to annual basis).

A comparison of the model fit for the weekly number of respiratory admissions without any mention of influenza or ILI and with (Figure 2A) or without pneumonia (Figure 2B) identifies a significant excess in pneumonia

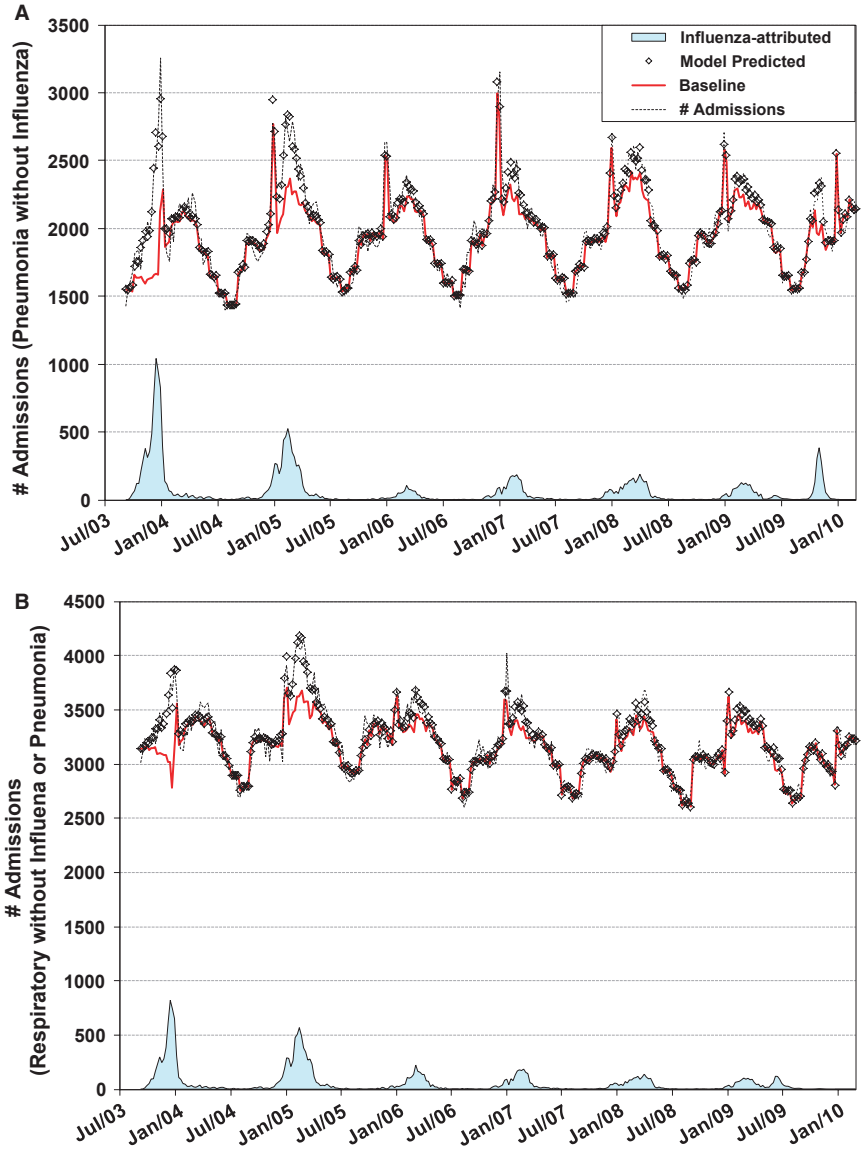

Figure 2. Respiratory admissions to hospital for urgent care, Discharge Abstract Database participating hospitals (Canada, excl Quebec) by presence of pneumonia. The weekly number of admissions (·····), model estimated baseline (——), and the weekly number of admissions predicted by the model (◇) are shown for respiratory admissions without any mention of influenza or influenza-like illness (ILI) and with (A) or without pneumonia (B). The area between the predicted and baseline curves is shown below (▭) and corresponds to the number of admissions attributed to influenza, but for which a diagnosis of influenza or ILI was not recorded in the patient's chart. During the fall pandemic wave, case ascertainment appears to have been nearly complete for patients with respiratory conditions other than pneumonia.

admissions during the fall wave, although among respiratory admissions without influenza or pneumonia no excess was identified during the same period. By MRD, most of the excess admissions were among patients admitted for respiratory conditions. During the pandemic, the number of excess secondary respiratory admissions was less than expected based on the background population prevalence of H1N1 (Table 1).

Age-specific hospitalization rates

The most notable improvement in ascertainment during the pandemic period occurred in the adult age groups (Figure 3A), although completeness during the pandemic period declined with increasing age. The multiplier ranged from an estimated 1·25 (1·1–1·4) for children under the age of 5 years to 2·1 (1·4–2·8) for persons 65 years of age or older (Figure 3B). Laboratory testing has been more routine among pediatric hospitalized patients than for adults in recent years[29] and this is reflected in the narrower gap between the rates of hospitalization coded and attributed to influenza. For younger age groups, the estimated number of admissions attributed to seasonal influenza was based on respiratory admissions excluding asthma and bronchiolitis, as including asthma and bronchiolitis admissions resulted in very large confidence intervals for the impact of influenza. (The impact of influenza on asthma and bronchiolitis admissions is likely to be relatively small,[24] and similar results were noted in earlier work.[19]) The effect of omitting these categories from the model appears to be minimal, as shown for the 10–14-year age group (Figure 3A). The influenza-attributed hospitalization rate for persons <65 years was an estimated 5·8 (95% CI, 3·1–8·4) times higher for H1N1/2009 than for previous H1N1 seasons. Rate ratios for H1N1/2009 to seasonal influenza (H3N2 and H1N1) were estimated by 5-year age groups (Figure 3C). Due to limited statistical power, rate ratios for H1N1/2009 to seasonal H1N1 alone were estimated for four age groups only: <50, 50–64, 65–74, and 75 years or older. With the exception of the 65–74-year age group, the rate ratios (5·9, 5·2, 2·1, and 0·2, respectively)

Table 1. Rates of hospital admissions attributed to seasonal and pandemic influenza, (2002/03–2009/10)

Diagnosis category	Seasonal influenza 2003/04–2008/09		H1N1/2009 pandemic	
	Rate/100 000	% of total respiratory	Rate/100 000	% of total respiratory
Influenza admissions by diagnostic code (any mention)				
J09 code (pandemic influenza)			29·1	54
J10 (influenza, virus identified)	5·2	15	3·9	7
J11 (influenza or ILI)*	2·9	8	8·1	15
Primary diagnosis of J10/J09	3·2	9	21·5	40
Any mention of influenza or ILI*	8·1	23	41·2	76
Respiratory admissions without any mention of influenza				
Pneumonia*	13·6	38	10·1	19
Other respiratory*	13·9	39	4·6	9
By most responsible diagnosis (MRD)				
Respiratory*	26·1	76	46·6	89
Non-respiratory MRD with a secondary respiratory diagnosis*	8·2	24	5·9	11
Expected background prevalence of influenza in admissions for non-respiratory causes**	5		9	
Total respiratory admissions*,***	35·2	100	54·0	100
Multiplier				
Influenza-attributed/influenza virus identified	6·8		1·6	
Number of respiratory admissions attributed to influenza†	12 000		18 000	

ILI, influenza-like illness.
*Denotes figures, which are model estimates or indirect estimates of the burden attributed to influenza. Admissions coded to J09 and J10 (influenza virus identified) are considered direct measures of the influenza burden. If any of the admissions coded to J09 or J10 were actually unrelated to the presence of the influenza infection, these admissions would be attributed to the baseline rather than the indirect or statistical estimate of the total respiratory admissions attributed to influenza.
**Using time off work as a proxy for population prevalence.
***Some of the subcategories detailed above may overlap.
†Projected to Canadian Population for 2009.

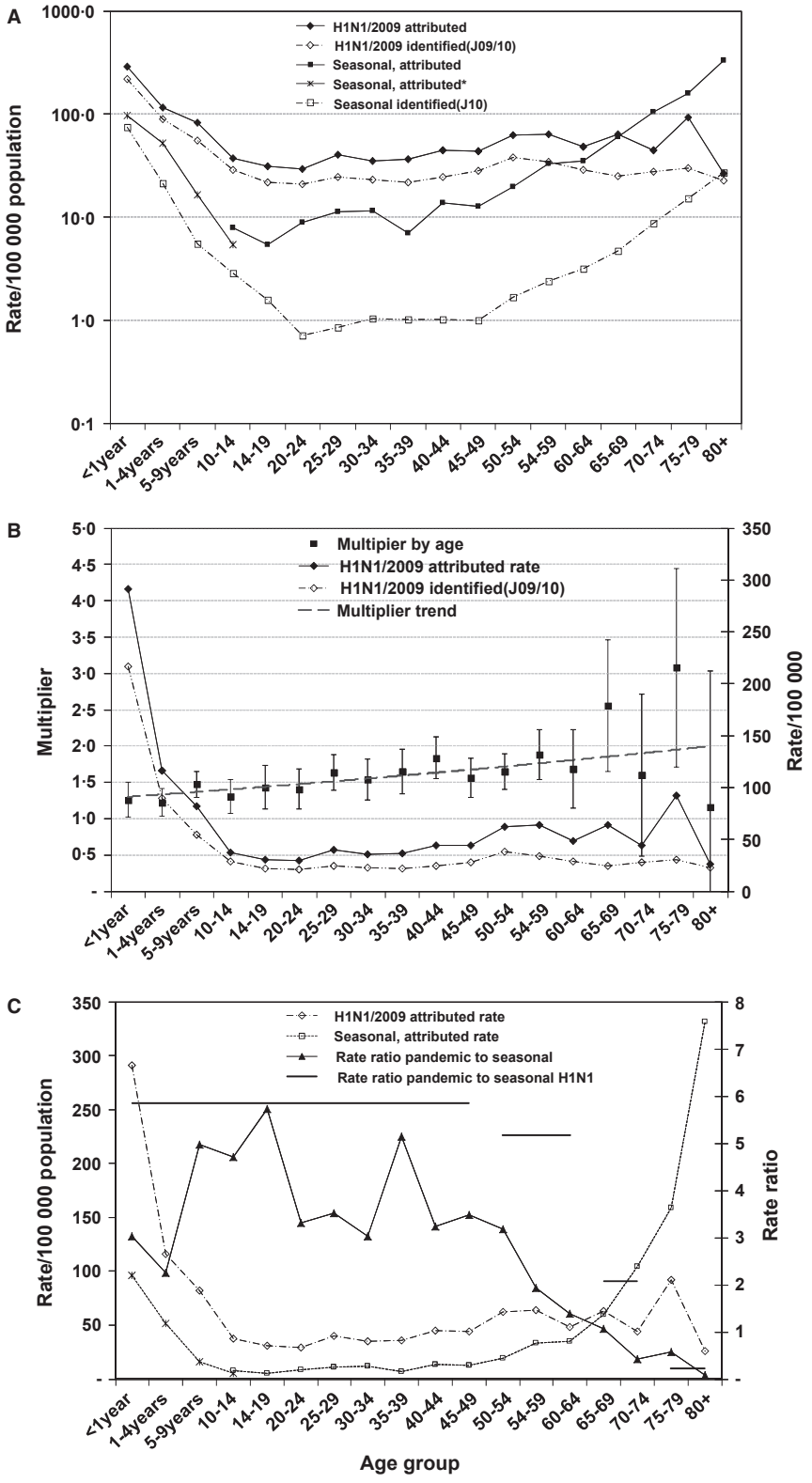

Figure 3. Hospitalization rates and multipliers for urgent care 2003/04–2009/10, Discharge Abstract Database participating hospitals (Canada, excludes Quebec), by age group. (A) Age-specific hospitalization rates for admissions with any mention of an identified influenza virus (J09, J10) are compared on a log scale with rates for admissions attributed to influenza for the seasonal and pandemic periods. In younger age groups, the influenza-attributed rates were based on excess respiratory admissions excluding asthma and bronchiolitis. (B) Multipliers by 5-year age group: admissions to hospital attributed to H1N1/2009 divided by J09 or J10 coded admissions, Canada. The multipliers increased with increasing age. (C) Ratio of the influenza-attributed rates for the pandemic period to the average for the seasonal period (2003/04–2008/09) is shown for 5-year age groups (–▲–). The corresponding rate ratio for the H1N1/2009 pandemic to the average annual rate for seasonal H1N1 was calculated for the following age groups: <50, 50–64, 65–74, and 75 years or older (– – for each age group).

were statistically different from 1·0 at the 5% significance level. For persons under the age of 50 years, H1N1/2009 pandemic admission rates were an estimated 5·9 (95% CI, 3·9–7·9) times higher compared with previous H1N1 seasons, whereas for persons aged 75 years or older, the ratio (0·2 with an upper 95% CI of 0·4) was notably lower.

Discussion

Rates of respiratory hospital admissions attributable to the H1N1/2009 pandemic strain were elevated compared with most previous seasons. More notably, hospitalization rates were four to eight times higher for persons under the age of 65 years during the H1N1/2009 pandemic compared with previous H1N1 seasons. Overall, estimated rates for the pandemic period were comparable to rates estimated for the 2003/04 (H3N2 A/Fujian/411/02) and 2004/05 seasons, although the impact was not uniform by age. In 2004/05, two antigenically distinct H3N2 strains, A/Fujian/411/02 and A/California/07/04, circulated.[27,30] The average seasonal rate for 2002/03–2008/09 is lower than previous estimates for the 1990's,[3] in part because the previous estimates included three particularly severe H3N2 A/Sydney seasons. For the working-age population, aged 20–64 years, hospitalization rates attributed to H1N1/2009 were an estimated 2·6 (95% CI, 2·4–2·9) times higher than the average for previous seasons (Figure 3), although differences in absenteeism rates were less notable.[2]

Our estimated multiplier of 1·6 (95% CI, 1·4–1·9) is considerably lower than the multiplier estimated at 2·7 for the United States[14] and a significant reduction from 6·8 for seasonal influenza in previous years. The higher multiplier in the United States has been attributed primarily to higher multipliers in some states with less complete ascertainment procedures and was calculated using different methods.[14] Recently published estimates of influenza-related hospitalization rates for the 2009 pandemic in the United States[31] were slightly higher than the Canadian estimate, although the US estimate was for a single county and confidence intervals for the estimates were much larger. Recently published estimates for seasonal influenza for the United States[32] were somewhat higher than our estimates, although these estimates were for the 1993–2008 period and our estimates for the earlier period were also higher.

In Canada, over half of the admissions attributed to H1N1/2009 were coded to J09. Although priority was given to sub-typing specimens from hospitalized patients, J10 still accounted for 11% of admissions with a J10 or J09 code. In comparison, 23% of the influenza A positive tests reported to *FluWatch* over the pandemic period were not sub-typed.[33] During the pandemic, there was a substantial increase in virus identification among clinically diagnosed patients; the use of J11 dropped from 36% to 20% of admissions with any mention of influenza or ILI.

During the fall wave, most of the missed H1N1/2009 admissions among respiratory patients were in patients with a diagnosis of pneumonia. As the estimated multipliers for seasonal influenza were also higher for respiratory patients diagnosed with pneumonia (details not shown), it is possible that pneumonia complications occurred with enough delay that many patients who were originally infected with influenza were no longer shedding significant quantities of virus, or that the attending physician was less likely to consider a diagnosis of influenza or ILI when pneumonia was present.

Although we expect similar improvements in the multiplier associated with deaths due to H1N1/2009 compared to seasonal influenza, there is still some uncertainty in the full H1N1/2009 mortality burden arising from the fact that most seasonal influenza deaths, even for age ranges that experienced a significant number of H1N1/2009 confirmed deaths, did not occur in hospital.[4]

Model fit

Various statistical models have been used to estimate the disease burden attributable to influenza. Most models use a form of Poisson regression and in most cases, results were found to be similar despite the model differences.[18,34,35] The main differences are in the choice of parameters to describe seasonality, the choice of a linear or logarithmic link, the choice of proxy variable for influenza activity, and the inclusion of proxy variables for the activity of RSV and other respiratory viruses. In this study, we chose a linear link for its face validity; that is, the weekly number of attributed cases should be proportional to the number of confirmed cases. A logarithmic link captures the multiplicative nature of seasonality over a period of substantial population growth better, but not the additive nature of influenza admissions. As observed by Thompson *et al.*,[18] results in our study were also robust to the removal of terms describing the activity of RSV, PIV-1, and other respiratory viruses or holidays. However, these reduced models had poorer model fit, a higher scale parameter value and, hence, larger confidence intervals for the influenza multipliers. The largest difference in estimates of the burden attributable to influenza came from removing the monthly indicator variables and leaving only the sinusoidal terms to explain seasonality. As the sinusoidal curve underestimated baseline seasonality for respiratory admissions for the months of April and May in the spring and September and October in the fall, the largest discrepancy was observed for influenza seasons with significant influenza activity in either the spring or fall. Using a sinusoidal function to describe seasonality may work in many situations; however, where possible, the sufficiency of the sinusoidal function should be tested in each situation.[36]

Although viral identification data have been traditionally used as the proxy variable for influenza activity, the availability of J10/J09 admissions under ICD-10 coding improved the model fit as well as providing better face validity. Once circulation of a novel strain with pandemic potential was announced in late April, testing increased sharply, and then varied in response to public health needs over the pandemic period. Although the percent positive is often used, as this approach would normalize for the unusually high testing rates early in the pandemic period, the use of this normalized variable did not capture peak influenza activity well in the Canadian setting.[3] The percent positive time series can also be strongly influenced by testing procedures and false-negative tests results,[12] which is likely contributed to the poor performance during periods of peak influenza activity. With laboratory confirmation in over 50% of admissions attributed H1N1, the expected precision of the model results for the pandemic period is fairly high. Uncertainty in comparing H1N1/2009 rates to seasonal H1N1 rates stems from the small number of seasonal H1N1 confirmed admissions (and viral identifications).

Despite efforts to assess potential sources of bias inherent in this ecological study, these estimates of the hidden disease burden attributed to influenza are still indirect estimates, and it is important to note that confidence intervals can be influenced by the choice of model and parameterization. There are other limitations as well. Although the introduction of ICD-10 coding provides viral identification data specific to the hospitalized population, a J09 code suggests, but does not guarantee, that this diagnosis was in fact laboratory confirmed as A/California/7/2009 H1N1. We were unable to successfully estimate the influenza burden among admissions coded to asthma, bronchiolitis, and croup in the pediatric population. Although all patients hospitalized with a confirmed H1N1/2009 infection were not necessarily admitted because of the infection, the regression modeling approach takes this into account by attributing only excess admissions to influenza with the rest absorbed by the baseline. Even so, not all of the excess respiratory admissions will be excess admissions. Approximately, 20% of admissions of patients with an identified influenza virus were coded to a non-respiratory condition as the primary reason for the hospital stay, and the influenza infection may have only complicated the stay. Noting that there was an associated decline in non-respiratory admissions during periods of peak influenza activity,[3] some uncertainty remains about what proportion of these admissions were truly due to the influenza infection. Nor do we have an explanation for why the excess in secondary respiratory admissions was less than expected during the pandemic based on population prevalence (Table 1). However, precise estimates of the clinical attack rate are not available and the calculation of the expected prevalence of laboratory confirmation among patients admitted specifically for non-respiratory conditions is only approximate. Also because of the decline in non-respiratory admissions associated with periods of influenza activity (not shown), estimates of the influenza burden among patients without a respiratory diagnosis was not possible using this approach. Studies that have shown an association with influenza and heart disease,[37,38] have generally not looked for respiratory co-diagnoses and our previous study on co-morbidities associated with in-hospital deaths suggests that respiratory conditions were likely noted in most non-respiratory deaths attributed to influenza.[4] And finally, the DAD does not include data for the province of Quebec, and Manitoba was still using ICD-9 coding for the 2003/04 season, although previous estimates of influenza rates by province suggest that provincial rates are similar.

In summary, a significant improvement in case ascertainment of hospitalized patients was observed for the pandemic period compared with seasonal influenza, although a slight hidden burden likely remains. Hospitalization rates for H1N1/2009 were significantly elevated compared with previous H1N1 seasons for persons under the age of 65 years. With over 50% of admissions attributable to H1N1/2009 coded to J09, uncertainties in the statistical estimates of the influenza burden are greatly reduced compared with previous estimates that used viral identifications from a general population as a proxy for the level of influenza activity. In exploring various model parameterizations, the largest difference in estimates of the burden attributable to influenza came from removing the monthly indicator variables and leaving only the sinusoidal terms to explain seasonality.

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Authors' contributions

DS and AM conceived the study. DS performed the analysis and drafted the manuscript. DS and KM contributed to the study design. All contributed to the interpretation of study results. All authors revised the manuscript critically, and all approved the final version that was submitted.

Potential conflicts of interest

None declared.

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