DOI:10.1111/j.1750-2659.2008.00035.x
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Original Article

Role of influenza and other respiratory viruses in admissions of adults to Canadian hospitals

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Accepted 13 September 2007.

Objective We sought to estimate age-specific hospitalization rates attributed to influenza and other virus for adults.

Methods Admissions from Canada's national hospitalization database (Canadian Institute of Health Information), from 1994/95 to 1999/2000, were modeled as a function of proxy variables for influenza, respiratory syncytial virus (RSV) and other viral activity, seasonality and trend using a Poisson regression model and stratified by age group.

Results The average annual influenza-attributed hospitalization rate for all adults, 20 years of age or older, over the study period, which included three severe seasons, was an estimated 65/100 000 population (95% CI 63–67). Among persons aged 65 and over, 270–340 admissions per 100 000 population per year were attributed to influenza, while 30–110, 60–90 and 130–350 per 100 000 were attributed to RSV, parainfluenza (PIV) and other respiratory viruses, respectively. Although marked season-to-season variation in age-specific hospitalization rates attributable to influenza was observed in persons 50 years of age and older, increasing risk with age was preserved at all time periods.

Conclusions Influenza, RSV, PIV and other respiratory viruses were all associated with morbidity requiring hospitalization, while influenza was responsible for peak respiratory admissions. The burden of health care utilization associated with respiratory viruses is appreciable beginning in the sixth decade and increases significantly with age.

Keywords Adults, hospitalization, influenza, para-influenza, respiratory syncytial virus.

Please cite this paper as: Schanzer *et al.* (2008) Role of influenza and other respiratory viruses in admissions of adults to Canadian hospitals. Influenza and Other Respiratory Viruses 2(1), 1–8.

Introduction

The annual winter surge in antibiotic utilization, ambulatory visits, hospitalization and mortality associated with respiratory illness has been attributed primarily to influenza virus infection.[1–3] Increasingly the contribution of other viruses, particularly respiratory syncytial virus (RSV) to respiratory morbidity in older adults is being recognized.[4–8] RSV is a leading cause of hospitalization for respiratory tract infection in young children.[9–12] Previous studies have estimated the mortality associated with influenza and RSV in adults,[4] and prospective surveillance studies of hospital admissions and ambulatory visits for laboratory-confirmed illness have elucidated the burden of illness and clinical spectrum of disease in certain settings.[5,13]

In Canada, detailed records of all hospital discharges have been captured in a national database since 1994. We aimed to use a statistical model to estimate the excess admissions attributable to these viruses at the national level and to determine the burden of illness associated with influenza-attributable illness in adults by age and by season, while estimating and controlling for the effects of other respiratory viruses, particularly RSV.

Methods

Sources of data

Weekly hospital admissions for persons over 19 years of age were extracted from the Canadian Institute of Health Information patient-specific Hospitalization Morbidity Database (HMDB)[14] for the period September 1994 to August 2000. The HMDB contains all cases separated (discharge or death) from a hospital in Canada. Each discharge record identifies the most responsible diagnosis (MRD) for the length of stay and up to 15 additional diagnostic fields. Diagnoses for this period were coded in accordance with

the *International Classification of Disease, Ninth Modification* (ICD-9-CM).[15] Records were aggregated to a weekly level by 5-year age groups and diagnostic group. The impact of influenza was estimated for various diagnostic groups, selected to illustrate their association with influenza. The diagnostic group of all primary respiratory admissions (MRD of ICD-9 460-496) was further divided into the following respiratory groups: influenza 487, pneumonia 480–486, acute respiratory infection 460–466, chronic obstructive pulmonary disease (COPD) 494–496, and asthma 493. As congestive heart failure (CHF) 428 was the only diagnostic category for which a strong association with influenza was found, it was included as a separate group. The remaining non-respiratory MRD admissions were divided into two categories where a secondary respiratory admission denoted a non-respiratory MRD admission with a respiratory complication noted in any of the 15 additional diagnostic fields.

Influenza-certified deaths (ICD-9 487) were obtained from the Canadian Vital Statistics Death Database.[16] Respiratory virus identifications were obtained from the Respiratory Virus Detection Surveillance System, Public Health Agency of Canada, which collects weekly data from selected laboratories on numbers of tests performed and numbers positive for influenza A, influenza B, RSV, PIV, and adenovirus. These specimens are submitted by clinicians in the course of clinical care and by sentinel physicians participating in the national influenza surveillance system *FluWatch*.[17] Denominators for the population at risk were obtained from Statistics Canada census and inter-census estimates.[18]

Statistical analysis

Weekly admissions, by diagnostic category and age group, were modeled using the Poisson regression model framework developed to estimate influenza-attributable hospitalization among children.[12] Poisson regression, similar to multiple linear regression, allows for natural variation in count data[19] and has been used in similar studies.[4,20] The general form of the model is shown in Figure 1. A regression approach facilitated the simultaneous estimation of the effects of influenza, RSV, PIV, and other viral activity on weekly respiratory admissions while controlling for other factors such as seasonality, holidays, the extended 3-week Christmas period, population growth, and secular trends toward generally reduced admission rates. The influenza year was defined as running from September to August. Influenza-attributed admissions were calculated as the difference between model-predicted admissions and the model-predicted admissions under the hypothetical absence of influenza (influenza activity variable set to zero). Census population counts were used to calculate rates. The positive predictive value was calculated for the 4 weeks of peak viral activity for each year as the number of influenza-attributable admissions divided by the total number of admissions.

Proxy variables for viral activity were developed similar to those used in the pediatric models. The three surrogate measures for influenza activity – influenza deaths, influenza (MRD) admissions (by age group), and laboratory-confirmed influenza identifications – described a very similar weekly pattern of activity. To account for season-to-season differences in the total number of specimens tested and for the relative severity of the strains circulating, the proxy variable for influenza activity (denoted as *Inflbase*) was calculated as influenza-attributed admissions (MRD) for each age group. This process normalized annual influenza laboratory confirmations to the annual level of hospital admissions, reflecting the variation in relative severity of the various strains and strain types (H3N2, H1N1, and B) by age group. Hence, *Inflbase* was similar to weekly

$$\hat{H}_w = \sum_{m=1}^{12} \beta_{1,m} \times Mon_{w,m} \quad \text{General seasonality}$$
$$+ \sum_{y=1995}^{2000} \beta_{2,y} \times FY_{w,y} \quad \text{General Trend}$$
$$+ \beta_3 \times Holiday_w \quad \text{General effect of a statutory holiday}$$
$$+ \beta_4 \times \text{Pre}\_Xmas_w \quad \text{Pre - Christmas period}$$
$$+ \beta_5 \times Xmas_w \quad \text{Christmas week Dec25 - Jan1}$$
$$+ \beta_6 \times Janww1_w \quad \text{Return to work week (week includes Jan 5)}$$
$$+ \beta_7 \times Sept1_w \quad \text{Indicator variable to account for asthma spike in mid Sept.}$$
$$+ \beta_8 \times Inflbase_w \quad \text{Influenza-attributed}$$
$$+ \beta_9 \times RSVbase_w \quad \text{RSV-attributed}$$
$$+ \beta_{10} \times PIV_w \quad \text{Para-influenza-attributed}$$
$$+ \beta_{11} \times Adeno_w \quad \text{Adeno virus-attributed}$$
$$+ \beta_{12} \times OtherILI_w \quad \text{Attributed to other ILI}$$

Figure 1. General form of the Poisson regression model used to model admissions for a variety of cause-specific and age-specific groups.

laboratory-confirmed influenza identifications, with additional weight given to strains that resulted in higher morbidity and mortality rates. For adults, the contribution of influenza B to the proxy variable for influenza activity was minimal. As no adult MRD category was strongly correlated with RSV identifications, the RSV proxy used in the pediatric model (RSV-attributed bronchiolitis admissions) was used as the RSV proxy for the adult models. This RSV proxy corrected for a general increase in the number of samples sent for laboratory identification, particularly from pediatric patients. Laboratory identifications for adenovirus and PIV were included in the model without further adjustment. It is worth noting that the seasonal pattern of PIV activity among adults was distinct from that for children. While the pediatric PIV proxy (related to croup admissions and likely PIV-1) was initially tested with the adult models, its effect was not statistically significant.

A substantial proportion of samples sent for viral identification were found to be negative. These negative identifications were assumed to be due to either other respiratory influenza-like infections, which we termed 'other ILI', or to false-negative results. The very strong association of the negative results with influenza and RSV confirmations necessitated the estimation and removal of false negatives. Using a similar Poisson regression model, negative samples attributed to influenza, RSV, PIV, or adenovirus were assumed to be false negatives.[21] Negative samples minus the model estimated false negatives were considered 'other ILI.' Results for adenovirus were combined with 'other ILI' to simplify reporting. While the proxies for RSV, PIV, and 'other ILI' have limitations, their inclusion in the model was primarily to assess and reduce the potential for bias in the estimates of influenza-attributed admissions.

Admissions by age group and diagnostic group were modeled separately. Hence, results presented here are the results of numerous regression models, and each estimated rate is an independent estimate. Where calculated, 95% confidence intervals are modeled-based. As a reminder that any bias or uncertainty, due in part to potentially omitted confounders or poor proxy variables for viral activity, is not captured in these calculations, the designation 95% MBCI (95% model-based confidence intervals) is used. SAS [19] PROC GENMOD was used for all model estimation. A linear link function was chosen to maintain a linear relationship between viral activity and attributed hospitalizations (a doubling of influenza activity results in a doubling of influenza-attributed admissions, not, for example, all respiratory admissions). To compensate for the use of linear link, dummy variables were used for the trend instead of a population offset, and the study period was kept short, so that monthly seasonality could be assumed to be constant over this period. As an alternative to the MBCI, influenza-attributed admissions were estimated using slightly different model forms (for example, including season specific coefficients for influenza activity, or the removal of the 'other ILI' covariate), providing a range, which was somewhat larger than the confidence intervals.

Results

Of an average 170 000 adult primary respiratory admissions per year, 14 000–17 000 admissions (or 8–10%) could be attributed to influenza, corresponding to an annual rate of 60–80 per 100 000 adult population. RSV, PIV and adenovirus each accounted for 2–3% of the annual adult respiratory admissions, and 'other ILI' another 4%. In total, these viruses accounted for an additional 20 000 admissions per year. Annual rates of admissions attributed to these viruses are summarized by age group in Table 1, where the range includes the range of variation that was observed by using slightly different model forms plus their 95% MBCI. The influenza-attributed rate corresponding to the model given in Figure 1 was 65/100 000 adult population per year (95% MBCI 63–67), and ranged from 20 to 92/100 000 for mild and severe seasons, respectively.

Average annual rates of admission attributable to influenza, RSV, parainfluenza, and 'other ILI' by 5-year age groups show that hospitalization rates are steady for all viruses until age 50–54 and then increase steadily (Figure 2). By age 65–69 there are over 100 hospitalizations per 100 000 population attributable to influenza and 80/100 000 attributable to RSV. By age 85 the average influenza-attributable hospitalization rate had increased to 650/100 000, while the effects of RSV remained relatively stable in older adults at 100/100 000.

Pneumonia was the main diagnostic category for influenza-attributable admissions at all ages (Table 2). RSV-attributed hospitalizations were most commonly associated

Table 1. Estimated average annual rate of respiratory admissions for adults attributed to influenza, RSV, PIV, adenovirus and other influenza like illness for 1994/1998–1999/2000, Canada

Virus	Rate/100 000			
	20–49 years	50–64 years	65+ years	20+ years
Influenza*	10–20	50–70	270–340	60–80
RSV	5–10	1–30	10–110	10–30
Parainfluenza	2–7	7–20	60–90	10–20
Adneovirus	3–8	5–20	30–90	10–20
Other ILI	7–20	10–60	100–260	30–60

RSV, respiratory syncytial virus; PIV, parainfluenza; ILI, influenza-like infection.
*Three of six seasons unusually severe for influenza.

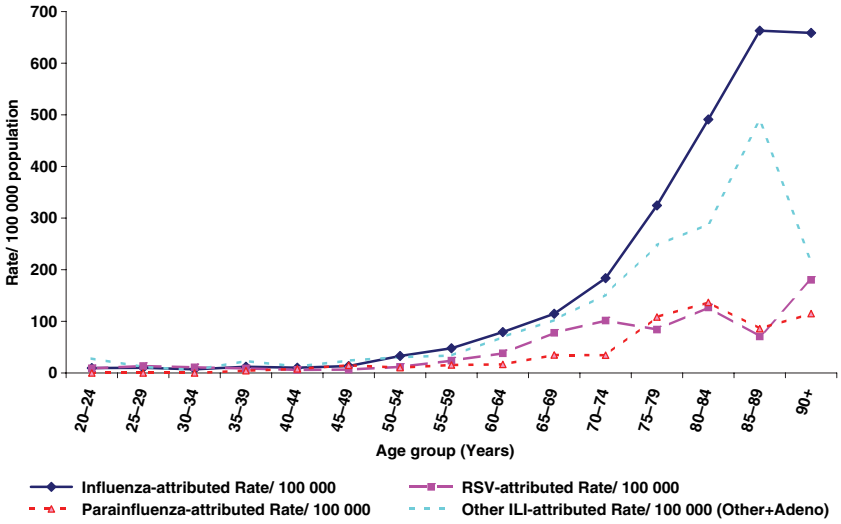

Figure 2. Hospital admission rates attributable to viral agent and 5-year age group for six respiratory seasons (1994/1995–1999/2000).

with a diagnosis of pneumonia in younger adults, but in those ≥65 years RSV was often associated with COPD, and other primary respiratory conditions (bronchitis, emphysema) as well as pneumonia.

Although a pneumonia MRD accounted for the largest proportion of influenza-attributable admissions (40% for seniors), a pneumonia MRD admission was no more predictive of influenza during peak activity than other respiratory MRDs. Of admissions for a chronic condition without any accompanying respiratory diagnosis, only admissions with an MRD of CHF were found to be associated with the level of influenza activity. For other admissions where the MRD was non-respiratory, an increase in admissions with respiratory complications was observed during periods of influenza activity, while admissions without any indication of respiratory complications decreased, as would be expected if some elective admissions were cancelled because of influenza, and other patients were admitted with influenza, but for other reasons (Table 2). The net reduction on all non-respiratory MRD admissions during periods of influenza activity was estimated to be only 0·1% of annual admissions.

Age-specific influenza-attributed rates, by an arbitrary classification of each season into mild, moderate, and severe, were plotted (Figure 3) to show the year-to-year variation in hospitalization rates. The three severe seasons (1997/98, 1998/99 and 1999/2000) were primarily H3N2 (A/Sydney), the moderate seasons (1994/95 and 1996/97) were also H3N2 seasons, while for the mild season (1995/96), H3N2 circulated very late in the season, and H1N1 was identified earlier in the season. In the oldest age groups rates varied by as much as sixfold. However, over all six inter-pandemic seasons, the same pattern of increasing hospitalization rates with older age was observed. The severe season curve is smoothest, as the study period included three severe seasons, two moderate, and only one mild season.

The excellent model fit is illustrated in Figure 4 where weekly respiratory admissions in adults over 65 years are plotted along with their predicted values, and the model-estimated baseline. The spike in admissions over the Christmas period is seen in the baseline curve, though not in influenza-attributed admissions. The seasonal pattern of influenza-attributed admissions is contrasted with admissions attributed to other viruses.

Discussion

The large burden of influenza in older adults, as indicated by utilization of hospital resources, is confirmed in this national study over six winter seasons. Notably, we have taken an approach that captures the burden of illness associated with institutional care that is hidden in clinical presentations not explicitly coded or recognized as being attributable to influenza infection, and have sought to account for the effect of other circulating respiratory viruses, particularly RSV. We also demonstrate a large season-to-season variation in influenza burden in which age-related risk is preserved among older adults. This variation highlights the need for the development of a nimble surge capacity in institutions during the winter respiratory season.

Previous work has demonstrated that influenza is probably the primary determinant of annual increases in winter-season mortality[22,23] and quantified the burden of mortality attributable to influenza and RSV.[4,7] Thompson *et al.* estimated influenza-attributable admissions using Poisson regression to model all respiratory admissions, and included a proxy for influenza activity but not other viral activity.[6] We found that the inclusion of proxy variables

Table 2. Estimated annual number of hospitalizations attributed to influenza, RSV, PIV, and other influenza-like illness by most responsible diagnoses for 1994/1998–1999/2000, Canada

Most responsible diagnosis (ICD-9)	Average annual admissions	Influenza-attributed*	RSV-attributed*	PIV-attributed*	Other ILI-attributed*	PPV† during peak activity (%)
Adults 20–49 years						
428 Congestive heart failure	1450					
460–466 ARI	3847	122	279	125		13
480–486 Pneumonia	10 033	454	472	288	597	17
487 Influenza	799	359	61			72
493 Asthma	8293	396	322	161	658	20
494–496 COPD	757					7
Other primary Resp 460–496	14 128	171	228		1517	6
Secondary respiratory 460–496	32 069	601	380	391	583	9
Non-respiratory‡	1 068 429	–1335			18 065	
Total primary respiratory	**37 857**	**1502**	**1362**	**574**	**2772**	**17**
Rate per 100 000	284	11	10	4	20	
Adults 50–64 years						
428 Congestive heart failure	7636					
460–466 ARI	1665	178	135			33
480–486 Pneumonia	9387	765	285	309	756	28
487 Influenza	483	284			56	81
493 Asthma	4172	294	156	161		25
494–496 COPD	4950	200	129	122	140	16
Other primary Resp 460–496	7834	454	294		536	24
Secondary respiratory 460–496	35 703	315			348	5
Non-respiratory‡	427 290	–1478			11 168	
Total primary respiratory	**28 491**	**2175**	**999**	**592**	**1488**	**28**
Rate per 100 000	839	51	23	14	35	
Seniors 65+						
428 Congestive heart failure	54 150	273	457		684	3
460–466 ARI	5116	745	442	236	556	39
480–486 Pneumonia	44 667	4088	923	976	3038	31
487 Influenza	1987	1418			108	84
493 Asthma	6245	450	327	153	179	26
494–496 COPD	22 802	1131	752	741	995	20
Other primary Resp 460–496	22 445	2165	994	410	1756	34
Secondary respiratory 460–496	128 859	2113	586		3568	9
Non-respiratory‡	806 911	–2824			18 847	
Total primary respiratory	**103 262**	**9997**	**3438**	**2516**	**6632**	**33**
Rate per 100 000	4354	284	108	70	202	

RSV, respiratory syncytial virus; PIV, parainfluenza; ILI, influenza-like infection; ARI, acute respiratory infections; COPD, chronic obstructive pulmonary disease.

*Significant at 5% level of significance.

†PPV is positive predictive value = influenza-attributable admissions/total admissions over four peak weeks of influenza activity.

‡Non-respiratory, excludes congestive heart failure above, and admissions with any secondary respiratory complication.

for RSV, PIV, and 'other ILI' activity resulted in only a marginal reduction in the number of admissions attributable to influenza. Notably, the inclusion of a proxy variable for 'other ILI' reduced the number of admissions attributed to RSV and these broader uncertainties due to model form are reflected in the broad ranges given in Table 1. A number of other model refinements contributed to a better model fit, and allowed us to estimate influenza-attributable admissions for subgroups with a smaller number of weekly admissions. Our influenza proxy based on the number of specimens confirmed positive for influenza, rather than proportion positive, captured peak influenza activity better, with implications for the selection of indicators of annual influenza activity. As evident in Figure 4, the baseline curve is not entirely sinusoidal, and the additional seasonal parameters captured the early autumn increase in asthma

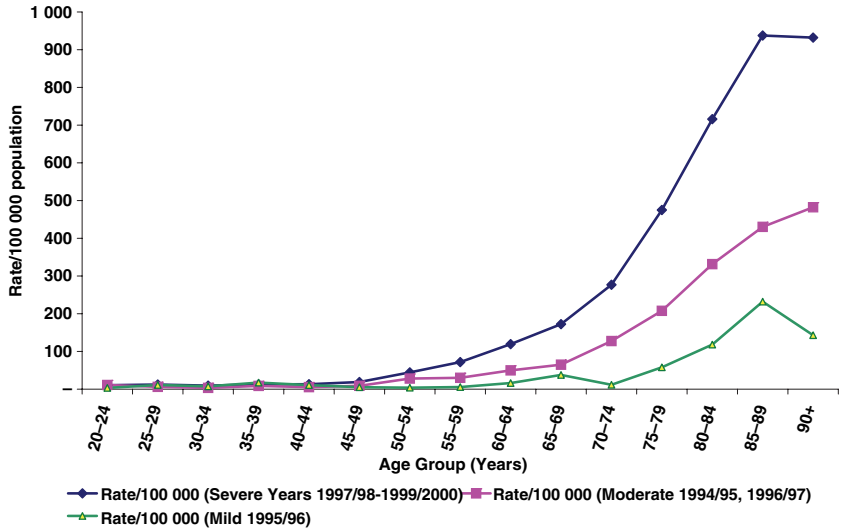

Figure 3. Age-specific influenza-attributed hospital admission rates by severity of influenza season over the 1994/1995–1999/2000 period.

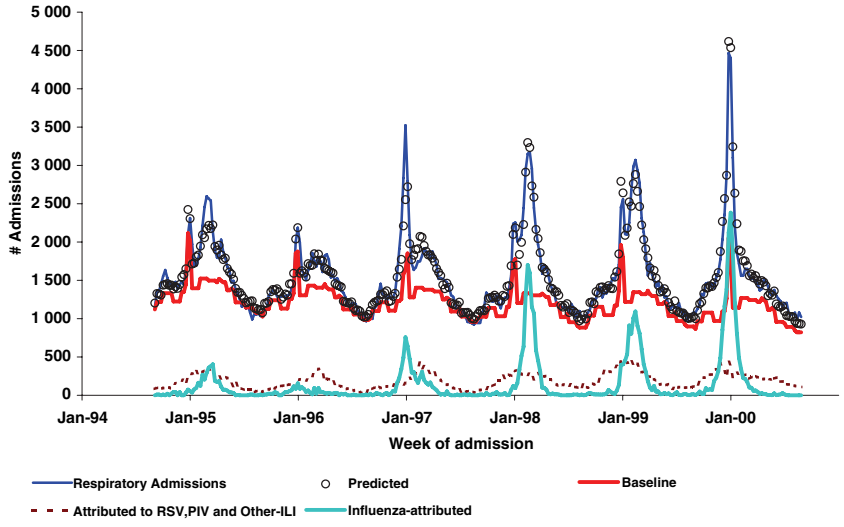

Figure 4. Weekly admissions for primary respiratory conditions and the attribution to influenza and other influenza like viruses among seniors aged 65+, Canada.

admissions, and holiday indicators captured the excess admissions over the Christmas period. That subgroup estimates (finer age or diagnostic groups) were consistent with group totals substantiates model validity. It is difficult to assess whether studies that have used the peri-seasonal baseline approach[24,25] were able to adequately correct for the seasonality of other viral agents or even other causes of seasonality.

Although the largest adult burden of influenza and RSV occurs in adults ≥65 years of age (270–340 and 30–110 admissions/100 000 population per year, respectively), the age-related increase in admissions begins in adults at age 50. Further analyses of co-morbidities should identify whether age >50 itself places a person at risk, or whether the risk is limited to persons with chronic illness. The United States includes this younger age group in its targeted annual influenza immunization program[26] because of an increased prevalence of high-risk conditions, as 50 is the age at which routine assessment and other preventive services are recommended, and because age-based strategies are thought to be more successful in increasing vaccine coverage than patient selection strategies based on medical conditions. However, in most of the 50 countries with government-funded national influenza immunization programs, including Canada, this group is not recommended for annual vaccine.[27] Targets for influenza vaccine coverage rates in persons over 65 have been met for 2001[28] in this country, suggesting that improving protection of this population will not be achieved through immunization alone. Other strategies to decrease the burden of influenza in the elderly include immunization of care-providers and other contacts, antiviral prophylaxis and treatment, and other infection control measures.[29,30]

Our study adds to the growing body of literature indicating that RSV is a significant cause of respiratory illness in older persons,[5,13,31,32] and is an appreciable cause of hospitalization as early as the sixth decade of life. In a review of etiologic studies of adult pneumonia hospitalizations, Han *et al.*[33] estimated that 2–9% of hospitalizations for pneumonia in adults over 65 years in the US are associated with RSV. While we found similar numbers of RSV-attributable admissions in patients with CHF, pneumonia, COPD and asthma as did Falsey *et al.* in a prospective laboratory-confirmed study,[5] we also identified RSV-attributable admissions among unspecified acute respiratory admissions (ICD-9 465) and acute as well as chronic bronchitis (Table 2). Improved case finding by clinicians and surveillance for RSV-associated illness in this age group would increase the accuracy of disease burden estimates. Our study confirms the value of an RSV vaccine for this older population.

Our study is limited by the lack of laboratory viral identification data specific to the hospitalized population by age group, and the expected poor test sensitivity for viral confirmation[34,35] complicated by a delay between onset of symptoms on clinical presentation.[36,37] Samples negative for influenza, RSV, PIV, and adenovirus are an incomplete surrogate for the many other viruses that circulate annually; however, working with this series was illustrative of the low sensitivities for routine laboratory tests as well as the potential for other viruses to cause considerable morbidity. PIV and adenovirus likely contribute to considerable adult respiratory morbidity, as well as other viruses such as rhinovirus and metapneumovirus that are known to cause illness in children.

Author contribution

Dena Schanzer, Joanne Langley and Theresa Tam conceived and designed the study. Dena Schanzer performed the analysis. Dena Schanzer and Joanne Langley drafted the manuscript. All authors revised the manuscript critically, and all approved the final version that was submitted.

Acknowledgements

Vital statistics data were provided to the Public Health Agency of Canada from the Canadian Vital Statistics databases at Statistics Canada with the knowledge and consent of the provincial and territorial vital statistics registries, which supply the data to Statistics Canada. Parts of this material are based on data and information provided by the Canadian Institute for Health Information. The authors acknowledge the support of the National *FluWatch* Network and the Data Coordination and Access Program of the Public Health Agency of Canada, and all those involved in the collection and compiling of this data. Their cooperation is gratefully acknowledged.

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